to ~pH2. The reaction mixture was then washed 3x with EtOAc. The organic phase was concentrated *in vacuo* and then diluted with 200mL aqueous MeOH. Oxone (10.02g, 14.57 mmol) was added in one portion and the reaction was stirred at room temperature for 4 hours. Conversion of sulfide to sulfone was monitored via LCMS. Upon completion, reaction was quenched by the addition of sodium thiosulfate. Salts were filtered, and the reaction mixture was washed 3X with ethyl acetate and dried over sodium sulfate. The organics were evaporated by vacuum under reduced pressure. Product was purified via HPLC. Yield: 1.1g, 23.1%. *m/z* (LCMS) M^+ 322.01, $R_f = 2.03$. δ_H 12.6 (1 H, br s), 3.5 (4 H, m), 3.5 (1 H, m), 3.4 (4 H, m), 3.25 (2 H, d), 3.0 (2 H, m), 2.9 (2 H, d), 2.4 (1 H, m), 1.3 (6H, d d).

Synthesis of 2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyric acid (28c)

4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (11.16g, 40.74 mmol) was dissolved in 100mL dry EtOH and set to stir at room temperature. NaOH pellets (4.81g, 120.25 mmol) were added in one portion, and the reaction mixture was allowed to stir for 10 min. Bromomethylcyclopropane (5.0g, 37.04 mmol) was then added, and the reaction mixture was allowed to stir at ambient temperature for 20 hours. Upon completion (LCMS), the reaction mixture was diluted with water and the pH was lowered to ~pH2. The reaction mixture was then washed 3x with EtOAc. The organic phase was concentrated *in vacuo* and then diluted with 200mL aqueous MeOH. Oxone (15.6g, 24.0 mmol) was added in one portion and the reaction was stirred at room temperature for 4h. Conversion of sulfide to sulfone was monitored via LCMS. Upon completion, reaction was quenched by the addition of sodium thiosulfate. Salts were filtered, and the reaction mixture was washed 3X with ethyl acetate and dried over sodium sulfate. The organics were evaporated by vacuum under reduced pressure. Product was purified via HPLC. Yield: 1.2g, 15.1%. *m/z* (LCMS) M^+ 320.1, $R_f = 1.84$. δ_H 12.6 (1 H, br s), 3.5 (4 H, m), 3.5 (1 H, m), 3.4 (4 H, m), 3.25 (2 H, d), 3.0 (2 H, m), 2.9 (2 H, d), 2.4 (1 H, m), 1.1 (1 H, m), 0.62 (2 H, q), 0.38 (2 H, q).

Synthesis of 2-(2-Difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyric acid (28d)

4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (1.27g, 4.64 mmol) was dissolved in 50mL dry EtOH and set to stir at room temperature. NaOH pellets (556mg, 13.92 mmol) were added in one portion, and the reaction mixture was allowed to stir for 10 min. 2-(Difluoromethoxy)-benzyl bromide (1.00g, 4.219 mmol) was then added, and the reaction mixture was allowed to stir at ambient temperature for 20h. Upon completion (LCMS), the reaction mixture was diluted with water and the pH was lowered to ~2. The reaction mixture was then washed 3x with EtOAc. The organic phase was concentrated *in vacuo* and then diluted with 100mL aqueous MeOH. Oxone (1.58g, 2.43 mmol) was added in one portion and the reaction was stirred at room temperature for 4h. Conversion of sulfide to sulfone was monitored via LCMS. Upon completion, reaction was quenched by the addition of sodium thiosulfate. Salts were filtered, and the reaction mixture was washed 3X with ethyl acetate and dried over sodium sulfate. The organics were evaporated by vacuum under reduced pressure. Product was purified via HPLC. Yield: 195mg, 19.0%. *m/z* (LCMS) M^+ 422.1. R_f = 2.42. δ_H 12.6 (1 H, br s), 7.6—7.2 (4 H, m), 7.19 (1 H, s) 4.5 (2 H, s), 3.5 (4 H, m), 3.5 (1 H, m), 3.4 (4 H, m), 3.2 (2 H, d), 2.75 (2 H, d).

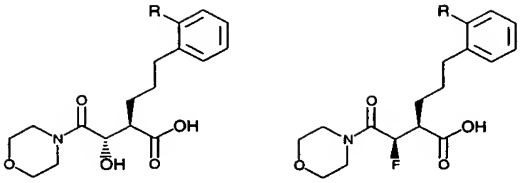
REFERENCE 29

(R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid (5a)

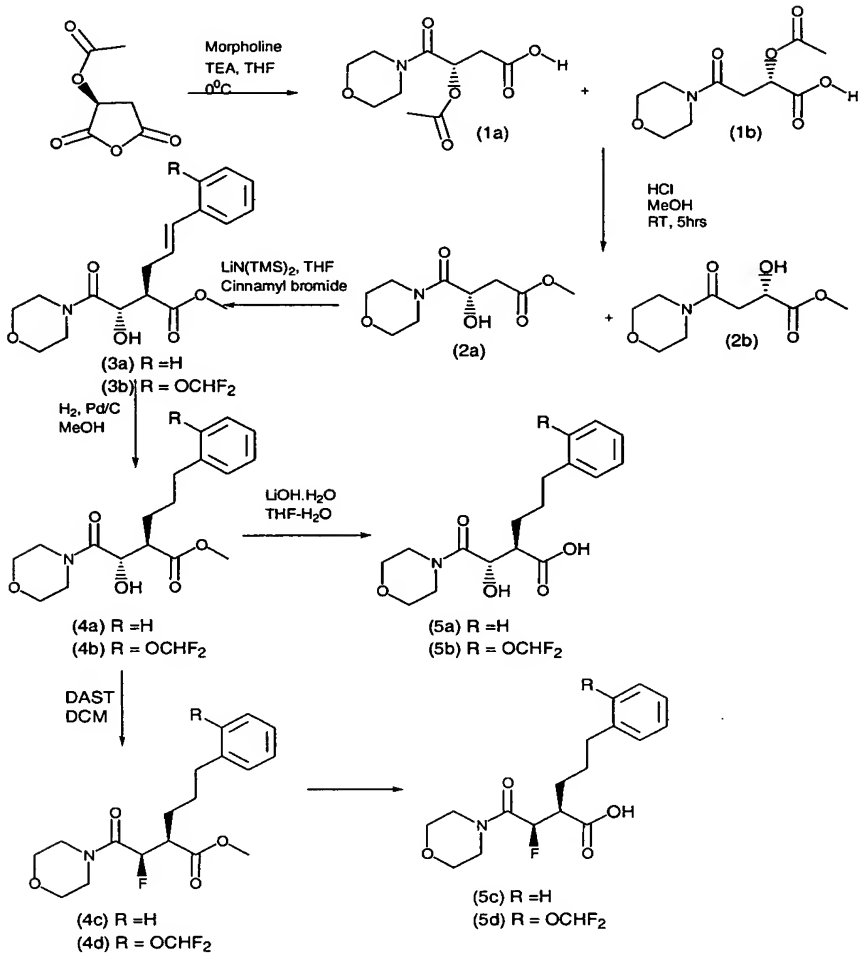
(R)-5-(2-Difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid (5b)

(R)-2-((S)-1-Fluoro-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid (5c)

(R)-5-(2-Difluoromethoxy-phenyl)-2-((S)-1-fluoro-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid (5d)



Compounds 5a, 5b, 5c and 5d were prepared according to the following reaction protocol:



5

(S)-3-Acetoxy-4-morpholin-4-yl-4-oxo-butyric acid (1a) &

(S)-2-Acetoxy-4-morpholin-4-yl-4-oxo-butyric acid (1b)

Morpholine (14.48 ml) and Triethylamine (23.14 ml, 166 mmol) were added to an

ice-cold solution of acetic acid (S)-2,5-dioxo-tetrahydro-furan-3-yl ester (25g, 158.12 mmol) in dry THF (600 ml) and the solution was stirred at room temperature over the week-end. Solvent was evaporated under reduced pressure, residue diluted with water, acidified to pH 2 with 1N HCl and extracted with ethyl acetate. Combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give a mixture of (S)-3-acetoxy-4-morpholin-4-yl-4-oxo-butyric acid and 2-acetoxy-4-morpholin-4-yl-4-oxo-butyric acid (14g) as colorless oil. MS: 246 (MH^+).

(S)-3-Hydroxy-4-morpholin-4-yl-4-oxo-butyric acid methyl ester (2a)

To a mixture of (S)-3-acetoxy-4-morpholin-4-yl-4-oxo-butyric acid and 2-Acetoxy-4-morpholin-4-yl-4-oxo-butyric acid (11g, 44.8 mmol) in dry methanol (30 ml) HCl in dioxane (4M, 7.3 ml, 29.16 mmol) was added and stirred at room temperature for 5 hrs. The reaction mixture was neutralized with solid $NaHCO_3$, filtered through a mixture of Celite/Na_2SO_4 (1:1) and concentrated under reduced pressure to give a mixture of (S)-3-Hydroxy-4-morpholin-4-yl-4-oxo-butyric acid methyl ester and (S)-2-Hydroxy-4-morpholin-4-yl-4-oxo-butyric acid methyl ester. Column chromatography on silica eluting with a mixture of ethyl acetate and methylene chloride gave (S)-3-Hydroxy-4-morpholin-4-yl-4-oxo-butyric acid methyl ester, (6 g) as white solid; ^1H NMR ($CDCl_3$) δ 2.62 (d, J=8Hz, 2H), 3.78-3.44 (m, 11H), 3.76 (d, J=9Hz, 1H), 4.8-4.73 (m, 1H); MS: 218(MH^+).

(E)-(R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl -pent-4-enoic acid methyl ester (3a)

Lithium hexamethyldisilazide (1M in THF, 14.5 ml, 14.5 mmol) was added to a solution of (S)-3-Hydroxy-4-morpholin-4-yl-4-oxo-butyric acid methyl ester (1.5g, 6.9 mmol) in dry THF (15 ml) at -78^0 C under N_2 and stirred for 30 min. Cinnamyl bromide (1.6g, 7.32 mmol) was then added, the reaction mixture stirred at $-78\ ^0$C for 2 hrs, warmed up to room temperature and stirred overnight at room temperature. The reaction was quenched with saturated ammonium chloride solution, adjusted the pH to 6 with 1N HCl and extracted with ethyl acetate. Combined ethyl acetate extracts were dried over $MgSO_4$

and concentrated under reduced pressure to give pale brown solid. Column chromatography on silica eluting with a mixture of ethyl acetate and methylene chloride gave the title compound as pale, yellow solid (1.15 g).

(E)-(R)-5-(2-Difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pent-4-enoic acid methyl ester (3b)

Similarly prepared according to the procedure above but replacing cinnamyl bromide with1- ((E)-3-Bromo-propenyl)-2-difluoromethoxy-benzene.

(2R,3S)-2-Benzyl-3-hydroxy-4-morpholin-4-yl-4-oxo-butyric acid methyl ester (3c)

Similarly prepared according to the procedure above but replacing cinnamyl bromide with benzyl bromide.

(R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid methyl ester (4a)

A solution of (E)-(R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pent-4-enoic acid methyl ester (1.55g, 4.65 mmol) in methanol (15 ml) was hydrogenated at 50 psi over Pd/C for 4 hrs. The catalyst was removed by filtration through celite and the filtrate concentrated under reduced pressure to give (R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid methyl ester as pale, brown solid (1.45 g); ^{1}H NMR ($CDCl_3$) δ 1.90-1.65 (m, 4H), 2.62-2.75 (m, 3H), 3.75-3.40 (m, 11H), 4.0 (d, J=15Hz, 1H), 4.47-4.4.39 (m, 1H), 7.38-7.15 (m, 5H); MS: 336(M^+).

(R)-5-(2-Difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid methyl ester (4b)

Similarly prepared according to the procedure above but using (E)-(R)-5-(2-

Difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pent-4-enoic acid methyl ester; ^{1}H NMR ($CDCl_3$) δ 1.93-1.58 (m, 4H), 2.78-2.58 (m, 3H), 3.80-3.42 (m, 11H), 4.03 (m, 1H), 4.44 (m, 1H), 6.53 (t, J=74Hz, 1H), 7.25-7.04 (m, 4H); MS: 402(MH^+).

(S)-2-((R)-1-Fluoro-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl -pentanoic acid methyl ester (4c)

(Diethylamino) sulfur trifluoride (2.0 ml, 15.2 mmol) was added to a ice cold solution of (R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid methyl ester (4a) (0.85 g, 2.5 mmol) in dry methylene chloride (15 ml) and the reaction mixture was stirred overnight while warming to room temperature. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with methylene chloride. The organic extracts were dried over $Na2SO_4$ and concentrated under reduced pressure. Column chromatography on silica eluting with a mixture of ethyl acetate and methylene chloride gave the title compound as an off-white solid (230 mg). ^{1}H NMR ($CDCl_3$) δ 1.90-1.58 (m, 4H), 2.78-2.57 (m, 2H), 3.28-3.10 (m, 1H), 3.75 (s, 3H), 3.74-3.45 (m, 8H), 5.40-5.12 (m, 1H), 7.35-7.18 (m, 5H); MS: 338(MH^+).

(R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid (5a)

A solution of (R)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid methyl ester (230 mg, 0.69 mmol) and $LiOH.H_2O$ (57.5 mg, 1.37 mmol) in a mixture of THF and water (2:1, 6 ml) was stirred at room temperature for 2.5 hrs. The reaction was diluted with water and THF removed under reduced pressure. The pH of the aqueous solution was adjusted to pH5 with 1N HCl and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give the title compound as white solid (180 mg); ^{1}H NMR ($CDCl_3$) δ 1.92-1.60 (m, 4H), 2.75-2.60 (m, 3H), 3.78-3.45 (m, 9H), 4.5 (d, J=8Hz, 1H), 7.35-7.18 (m, 5H); MS: 322(MH^+).

(R)-5-(2-Difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin

-4-yl-2-oxo-ethyl)-pentanoic acid (5b)

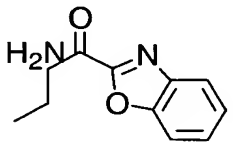
Similarly prepared according to the procedure above but using (R)-5-(2-difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid methyl ester; ^{1}H NMR ($CDCl_3$) δ 1.90-1.65 (m, 4H), 2.77-2.68 (m, 3H), 3.70-3.53 (m, 9H), 4,51 (d, J=4.4Hz, 1H), 6.52 (t, J=74Hz, 1H), 7.28-7.14 (m, 4H); MS: 388(MH^+).

(2R,3S)-2-Benzyl-3-hydroxy-4-morpholin-4-yl-4-oxo-butyric acid (5e)

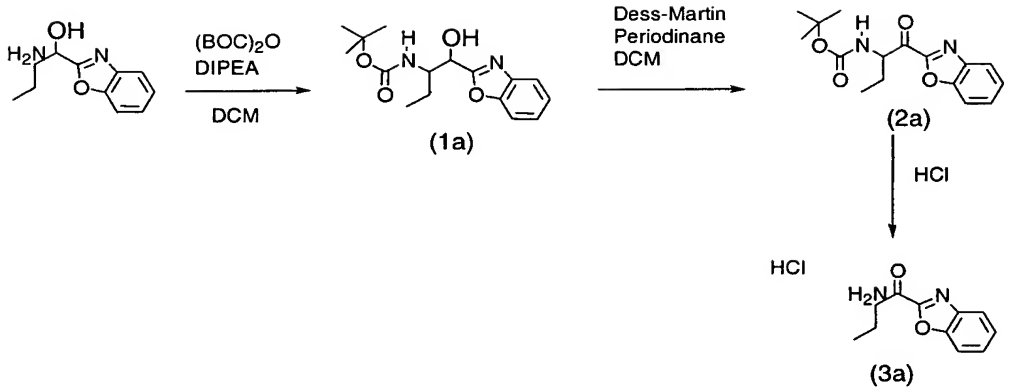
Similarly prepared according to the general procedure above but using (2R, 3S)-2-Benzyl-3-hydroxy-4-morpholin-4-yl-4-oxo-butyric acid methyl ester; ^{1}H NMR ($CDCl_3$) δ 2.90 (m, lH), 3.10 (m, 2H), 3.70-3.15 (m, 8H), 3.75 (m, 1H), 4.32 (d J=7.5Hz, 1H), 7.38-7.25 (m, 5H); MS: 294 (MH^+).

REFERENCE 30

2-Amino-1-benzooxazol-2-yl-butan-1-one



2-Amino-1-benzooxazol-2-yl-butan-1-one was prepared according to the following reaction protocol:



[1-(Benzooxazol-2-yl-hydroxy-methyl)-propyl]-carbamic acid tert-butyl ester (1a)

DIPEA (0.35 ml, 2 mmol) and di-tret-butyl dicarbonate (355 mg, 1.63 mmol) were added to a solution of 2-Amino-1-benzooxazol-2-yl-butan-1-ol (320 mg, 1.55 mmol) in dry methylene chloride (10 ml) and stirred at room temperature for 4 hrs. The reaction was quenched with saturated aqueous NH_4Cl and the pH was adjusted to neutral. Oraganic layer separated and the aqueous layer extracted with methylene chloride. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give, 1-(Benzooxazol-2-yl-hydroxy-methyl)-propyl]-carbamic acid tert-butyl ester (500 mg).

[1-(Benzooxazole-2-carbonyl)-propyl]-carbamic acid tert-butyl ester (2a)

Dess-Martin Periodinane (15% in DCM, 3.1 mmol) was added to a solution of, 1-(Benzooxazol-2-yl-hydroxy-methyl)-propyl]-carbamic acid tert-butyl ester in dry methylene chloride (15 ml) and stirred at room temperature for 4 hrs. A solution of $Na_2S_2O_3$ in aqueous $NaHCO_3$ was added and stirred at room temperature. Organic layer was separated and the aqueous was extracted with methylene chloride. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a pale brown solid. Column chromatography on silica eluting with a mixture of methylene chloride and heptane gave the title compound as off white solid (380 mg).

2-Amino-1-benzooxazol-2-yl-butan-1-one hydrochloride (3a)

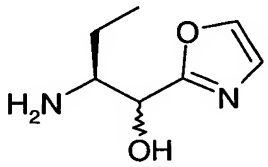
Hydrogen chloride in dioxane (1M, 1 ml) was added to a solution of, 1-(Benzooxazole-2-carbonyl)-propyl]-carbamic acid tert-butyl ester (2a) in dry methylene chloride (3 ml) and stirred at room temperature for 4 hrs. Concentration under reduced pressure gave the title compound as white solid (65 mg); ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J=7.5Hz, 3H), 2.20-2.05 (m, 2H), 4.96 (m, 1H), 7.58 (t, J=7.4Hz, 1H), 7.69 (t, J=7.4Hz, 1H), 7.94 (d, J=8.2Hz, 1H), 8.04 (d, J=8.2Hz, 1H), 8.75 (m, 3H); MS: 207(MH^+).

(1-Amino-cyclopropyl)-oxazol-2-yl-methanone hydrochloride (3b)

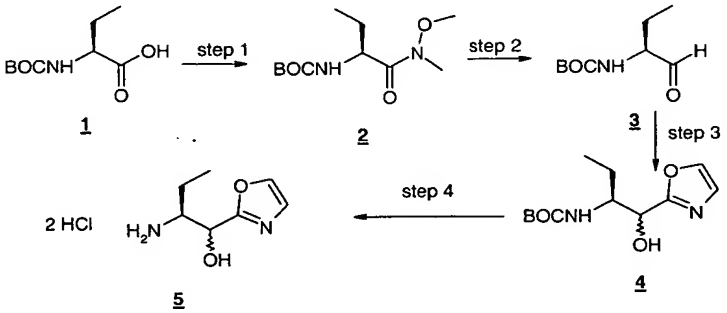
^{1}H NMR (DMSO) δ 1.79 (m, 2H), 1.22 (m, 2H), 7.58 (s, 1H), 8.49 (s, 1H), 9.22 (m, 3H); MS: 153(MH^+).

REFERENCE 31

2-Amino-1-oxazol-2-yl-butan-1-ol



2-Amino-1-oxazol-2-yl-butan-1-ol was prepared according to the following reaction scheme:



Step 1

To a stirring solution of of the BOC-L-α-aminobutyric acid (1, 17.75g, 87.3mmol) in dry methylene chloride (35ml) was added DIEA (33.45ml) followed by the N,O-dimethylhydroxylamine hydrochloride (9.37g, 96.03mmol) and PYBOP (50.0g, 96.03mmol). The reaction mixture was stirred overnight at room temperature. After the solvent was removed in vacuo, the oily residue was dissolved in ether and the precipitate which formed was filtered and the filtrate was concentrated to give 35.0g of a brown oil. The residue was dissolved in ethyl acetate and washed twice with 0.05N HCl, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and concentrated to give 14.0g of the product 2, which was used without further purification.

Step 2

Compound 2 (8.4g, 34.1mmol) was then dissolved in 30 ml of dry THF and cooled to -50° C under nitrogen, then LAH (1.0 M in THF, 37.5ml, 37.51mmol) was added drop wise over 30 minutes. The reaction was stirred for 1.5 hours at –50 ° C then allowed to warn to 0 ° C over 45 minutes. Then NaHSO4 (6.12g, 44.33mmol) was added slowly followed by cold water (2.0ml) and stirring was continued for 30 minutes. The reaction was filtered through celite, which was washed with methylene chloride. The volatiles were removed from the filtrate in vacuo. The solid residue was dissolved in ethyl acetate and washed with cold 0.05N HCl, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated to give 6.5 grams of compound 3 as colorless oil.

Step 3

Triethylborane (1.0 M in THF, 149.5ml, 149.5mmol) was added to oxazole (10.33g, 149.5mmol) and stirred for 45 minutes at room temperature. The mixture was then cooled to –78 ° C and n-BuLi (2.5 M in hexane, 59.8ml, 149.5mmol) was added dropwise and allowed to stir for one hour under nitrogen. Compound 3 (8.0g, 42.7mmol) was dissolved in 25 ml of THF and added to the reaction mixture. The reaction was stirred for 5 hours at –78 ° C then it was allowed to warm to 0 ° C for one hour. The reaction was then cooled back to –78 ° C and quenched with 7% acetic acid in ethanol (700ml) which

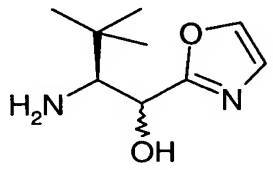
was allowed to stir overnight at room temperature. The mixture was concentrated in vacuo and the residue was dissolved in ether and filtered. The filtrate was concentrated in vacuo and the residue was dissolved in ethyl acetate washed twice with 0.005 N HCl, twice with sat'd sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified on silica using 10-40% ethyl acetate/heptane to give 3.85 grams of pure product **4**.

Step 4

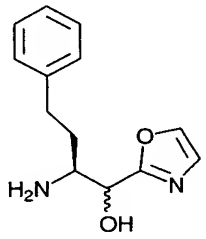
To a solution of compound **4** (1.1g, 4.29mmol) in dry methylene chloride (10.0ml), stirring under nitrogen at room temperature, was added 4M HCl (in dioxane, 10.73ml) dropwise followed by 5 ml of methanol. The reaction was stirred overnight then concentrated in vacuo to give 1.2 grams of compound **5** as a brown solid.

The following reference compounds were prepared according to the protocol described in Reference 31:

2-Amino-3,3-dimethyl-1-oxazol-2-yl-butan-1-ol



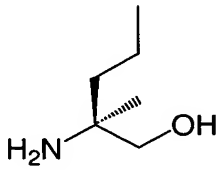
2-Amino-1-oxazol-2-yl-4-phenyl-butan-1-ol



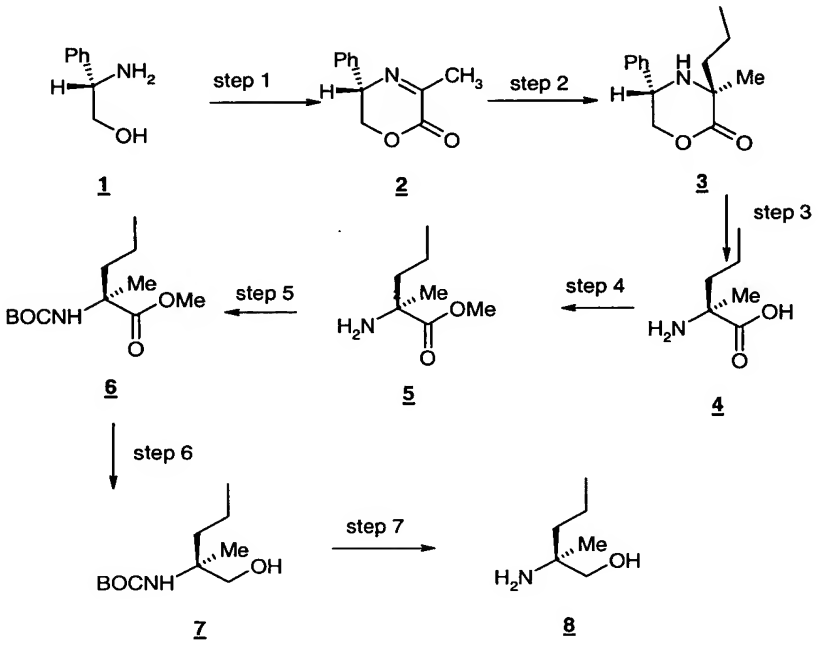
LCMS retention time 1.10 minutes; M+1 (233.1)

REFERENCE 32

2-Amino-2-methyl-pentan-1-ol



2-Amino-2-methyl-pentan-1-ol was prepared according to the following reaction scheme:



Step 1

S-(+)-Phenylglycinol (**1**, 25g,182mmol) was dissolved in trifluoroethanol (250ml) and ethyl pyruvate (23.3g, 200mmol) was added (exothermic) followed by molecular seives (4 angstroms) and the reaction was refluxed overnight. The reaction was filtered and concentrated to an oil. The oil was purified on a 500 g silica gel column and eluted with 3:1 heptane/ethyl acetate to give 19.94 grams of compound **2**.

Step 2

Compound **2** (15.0g, 79mmol) was dissolved in THF (400ml) and cooled to –78 °

C, the boron trifluoride etherate (22.4g, 158mmol) was added over a 15 minute period. The reaction was allowed to stir at –78 degree C for 2 hours and propyl magnesium chloride (2.0 M in ether, 79ml, 158mmol) was added over a one hour period and allowed to stir for 4 hours at –78 ° C. The reaction was allowed to warm to room temperature and stir overnight. The mixture was carefully quenched with sat'd NaHSO4 until pH of 8 was obtained. The reaction was extracted with ethyl acetate (2x200ml), then washed with water, brine, dried over sodium sulfate and concentrated to dryness. The residue was purified on silica eluting with 4:1 heptane/ethyl acetate to give 12.2 grams of compound **3**.

Steps 3 and 4

Compound **3** (9.0g, 39mmol) was dissolved in ethanol (100ml) and water (20ml) followed by the addition of 9 grams of Pd(OH)2 and TFA (4ml). The mixture was hydrogenated at 50 psi for 48 hours, then the reaction was filtered through celite which was concentrated to give 9 grams of crude material **4** which was used without further purification. Compound **4** was dissolved in dry methanol (300ml) and HCl gas was bubbled through for 15 minutes. The reaction was stirred at room temperature for three days and was concentrated. The crude product was purified on silica eluting With 1:1 heptane/ethyl acetate to give 3.9 grams of compound **5**.

Step 5

A mixture of compound **5** (3.9g, 27mmol), (BOC)2O (5.88g, 27mmol), and TEA (7.56ml, 54mmol) in 100 ml of dioxane and 100ml of water were stirred overnight at room temperature. The reaction mixture was concentrated and dissolved in ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The crude product was purified on silica eluting with 30 ethyl acetate/heptane to give 6.68 gram of pure product **6**.

Step 6

A solution of compound **6** (6.68g, 27mmol) in 200ml of THF was cooled to 0 ° C and LAH (1.0M in THF, 32.4ml, 32.4mmol) was added dropwise and the reaction was stirred for 30 minutes then allowed to come to room temperature. The reaction was stirred

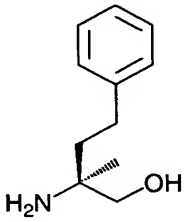
for another 30 minutes and the reaction was quenched with a solution of NaHS04, the THF was removed in vacuo and the residue was extracted with ethyl acetate which was washed with brine and concentrated. The product was purified on silica eluting with n-heptane to 5% methanol/ethyl acetate to give 2.8767 g of compound **7**.

Step 7

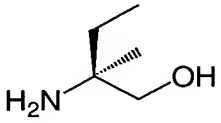
Compound **7** (0.5g) was dissolved in 5 ml of 4N HCL in dioxane and stirred for 1 hour at room temperature. The reaction was concentrated and dried under high vacuum to give 0.3859g of compound **8**, which was used without further purification.

The following reference compounds were prepared according to the protocol described in Reference 32:

2-Amino-2-methyl-4-phenyl-butan-1-ol

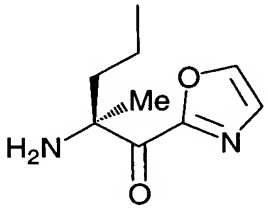


2-Amino-2-methyl-butan-1-ol

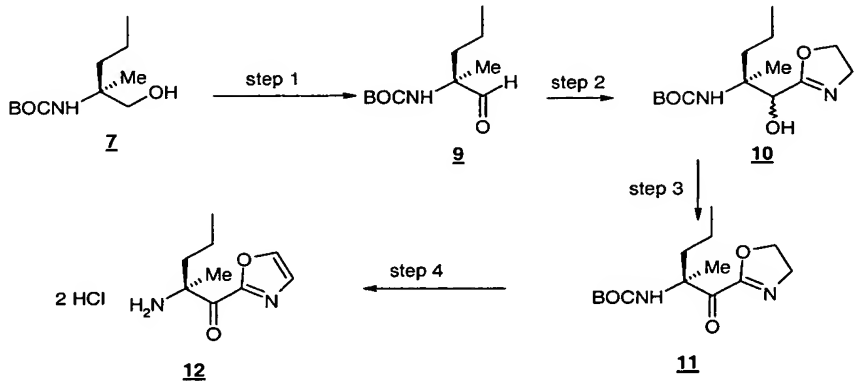


REFERENCE 33

2-Amino-2-methyl-1-oxazol-2-yl-pentan-1-one



2-Amino-2-methyl-1-oxazol-2-yl-pentan-1-one was prepared according to the following reaction scheme:



Step 1

A solution of oxalyl chloride (2.0M in CH2Cl2, 1.5ml, 3mmol) in 5 ml of methylene chloride was cooled to –78 ° C, then DMSO (0.44ml) was added drop wise to the mixture and allowed to stir for 5 minutes. A solution of compound **7** (Scheme 2, 0.4346g, 2.0mmol) in 10 ml of methylene chloride was added drop wise. The reaction was stirred at –78 degree C for 15 minutes and TEA (1.12ml, 8mmol) was added dropwise and the reaction was stirred for 2 hours at room temperature. The reaction was quenched with water and the product was extracted with ethyl acetate, then organic layer was washed with brine and the solvent was removed in vacuo. The crude product was purified on silica eluting with heptane to 10% ethyl acetate/heptane to give 0.3131 g of pure compound **9**.

Step 2

Triethylborane (1.0 M in THF, 4.84ml, 4.84mmol) was added to oxazole (0.3355g, 4.84mmol) in 4 ml of THF and stirred for 30 minutes at room temperature. The mixture was then cooled to –78 ° C and n-BuLi (1.6 M in hexane, 3.025ml, 4.84mmol) was added dropwise and allowed to stir for one hour under nitrogen. Compound **9** (0.2615g, 1.21mmol) was dissolved in 5 ml of THF and added to the reaction mixture. The reaction was stirred for 5 hours at –78 ° C, then quenched with 5% acetic acid in ethanol (20ml) which was allowed to stir overnight at room temperature and concentrated in vacuo. Ether was added and the solid was filtered and the filtrate was concentrated and the crude product

was purified on silica using 0-20% ethyl acetate/heptane to give 0.2528 grams of pure product **10**.

Step 3

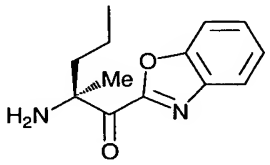
Dess-Martin periodinane (15% in CH2Cl2, 4.95g, 1.8mmol) was added to a stirring added to a stirring solution of compound **10** (0.2528g, 0.89mmol) in 5 ml of methylene chloride. The reaction was stirred at room temperature for 3 hours, then the reaction was quenched with a solution of sodium thiosulfate in sat'd sodium bicarbonate. The product was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified on silica eluting with 1:1 ethyl acetate/heptane to 5% methanol/ethyl acetate to give 0.2307 g of pure compound **11**.

Step 4

Compound **11** (0.2123g, 0.75mmol) was dissolved in 5 ml of 4N HCL in dioxane and stirred for 1 hour at room temperature. The reaction was concentrated and dried under high vacuum to give 0.1713g of compound **8**, which was used without further purification.

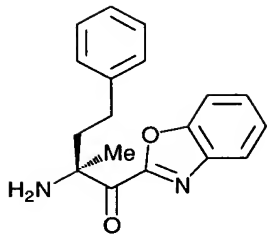
The following reference compounds were prepared according to the protocol described in Reference 33:

2-Amino-1-benzooxazol-2-yl-2-methyl-pentan-1-one



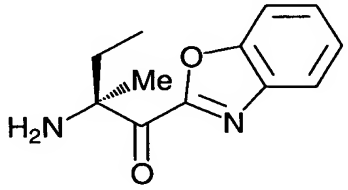
LCMS retention time 2.45 minutes; M+1 (233.1).

2-Amino-1-benzooxazol-2-yl-2-methyl-4-phenyl-butan-1-one



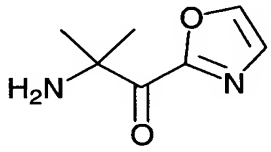
LCMS retention time 2.79 minutes; M+1 (295.1)

2-Amino-1-benzooxazol-2-yl-2-methyl-butan-1-one



LCMS retention time 2.29 minutes; M+1 (219.1)

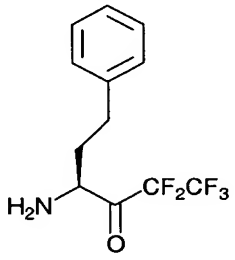
2-Amino-2-methyl-1-oxazol-2-yl-propan-1-one



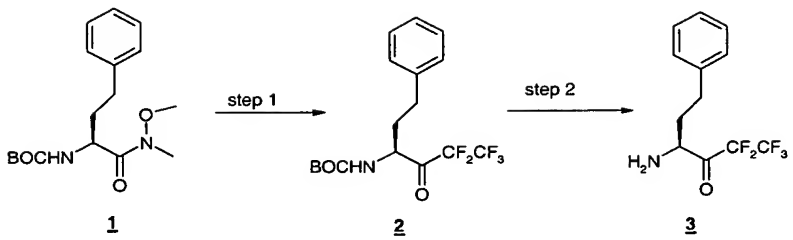
LCMS retention time 1.63 minutes; M+1 (155.1)

REFERENCE 34

2-Amino-4-phenyl-butyramide



2-Amino-4-phenyl-butyramide was prepared according to the following reaction scheme:



Step 1

Compound **1** (5g, 15.5mmol) was dissolved in dry ether (150ml) and cooled to –20° C, then perfluoroethyl iodide (25g, 100mmol) was bubbled into the mixture. The solution was then cooled to –50° C and methyl lithium/lithium bromide complex was added over a 30 minute period. The reaction was stirred for 1.5 hours at this temperature and was then quenched with acetone. After stirring for 15 minutes the reaction was diluted with ether (100ml) and poured onto 100ml of water contain KHSO4. The organic layer was separated and washed with water, brine, dried over sodium sulfate and concentrated to dryness. The material was purified on silica eluting with 1:1 ethyl acetate/heptane to give 1.7 grams of compound **2**.

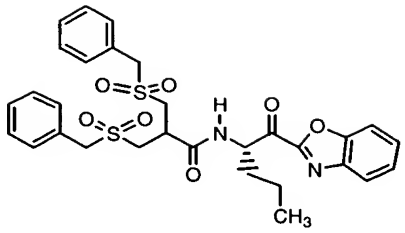
Step 2

Compound **2** (0.35g) was dissolved in 4 ml of 4N HCL in dioxane and stirred for 1 hour at room temperature. The reaction was concentrated and dried under high vacuum to give 0.2807g of compound **3** which was used without further purification; LCMS retention time 4.19 minutes; M+1 (282.1).

EXAMPLE 1

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide

(Compound 1)



A mixture comprised of 3-benzylsulfanyl-2-benzylsulfanylmethyl-propionic acid (0.239g, 0.719 mmol), prepared as in Reference 1, in methylene chloride (6 mL), HOBt hydrate (0.11g, 0.719 mmol), EDC (0.18g, 0.939 mmol), hydroxy amine (0.19 g, 0.86 mmol) and 4-methylmorpholine (0.075 mL) was stirred at room temperature for 1 hour and then poured into cold 1N aqueous hydrochloric. The product was extracted with ethyl acetate and the extracts were washed with saturated aqueous sodium chloride and then dried over magnesium sulfate. The solvent was removed by rotary evaporation at reduced pressure and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane to give *N*-[(S)-1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-butyl]-3-benzylsulfanyl-2-benzylsulfanylmethyl-propionamide (0.217 g).

A solution of *N*-[(S)-1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-butyl]-3-benzylsulfanyl-2-benzylsulfanylmethyl-propionamide (0.317 g, 0.594 mmol) in methanol (30 mL) was treated with a solution of Oxone® (0.913 g, 1.48 mmol) in water (20 mL) and then stirred at room temperature for 7 hours. The methanol was removed by evaporation at reduced pressure and the resulting suspension was diluted with water and the product extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium chloride and then dried over magnesium sulfate. The solvent was removed by rotary evaporation at reduced pressure and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane to give *N*-[(S)-1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-butyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide (0.143 g, 41% yield).

A solution of *N*-[(S)-1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-butyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide (0.140 g, 0.234 mmol) in methylene chloride (5 mL) was treated with 1,1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (0.127 g, 0.30 mmoL) and the resulting solution was stirred at room temperature for 30 minutes. Aqueous sodium thiosulfate and sodium bicarbonate

(15 mL, 0.25 M) were added and the reaction mixture was stirred for 20 minutes. The product was extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium chloride and then dried over magnesium sulfate. The solvent was removed by rotary evaporation at reduced pressure and the residue was crystallized from t-butylmethyl ether to give *N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-3-benzylsulfonyl-2-benzyl-sulfonylmethyl-propionamide (0.103 g, 74%); NMR (DMSO): 9.15 (d, J=6Hz, 1H); 8.01 (d, J=7Hz, 1H); 7.89 (d, J=8Hz, 1H); 7.65 (t, J=7Hz, 1H); 7.54 (t, J=8Hz, 1H); 7.37 (m, 10H); 5.36 (m, 1H); 4.5 (m, 4H); 3.68 (m, 1H); 3.45-3.25 (m, 4H); 1.95 (m, 1H); 1.73 (m, 1H); 1.47 (m, 2H); 0.91 (t, J=7Hz, 3H); MS: M(H+) 597.0 (596.17);

The following compounds were prepared by the method of Example 1 by substituting the required carboxylic acid in place of 3-benzylsulfanyl-2-benzylsulfanylmethyl-propionic acid:

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-(2-trifluoromethyl-benzylsulfonyl)-2-(2-trifluoromethyl-benzylsulfonylmethyl)-propionamide (Compound 2); ^{1}H-NMR ($CDCl_3$) δ: 7.93 (m, 1H); 7.69 (m, 4H); 7.4-7.6 (m, 6H); 7.20 (m, 2H); 5.58 (m, 1H); 4.54 (m, 4H); 3.69 (m, 1H); 3.30-3.55 (m, 4H); 1.55-1.90 (m, 1H); 1.45 (m, 1H); 1.32 (m, 2H); 0.90 (m, 3H); MS: M(+) 733.0; M(-) 731.6;

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-pentyl]-4-(2-methoxy-benzenesulfonyl)-2-[2-(2-methoxy-benzenesulfonyl)-ethyl]-butyramide (Compound 3); ^{1}H-NMR (DMSO) δ: 8.65 (d, 1H); 7.99 (d, J=7Hz, 1H); 7.89 (d, J=8Hz, 1H); 7.8-7.5 (m, 6H); 7.3-7.1 (m, 4H); 5.25 (m, 1H); 3.90 (m, 9H); 3.3 (m, 6H); 1.6 (m, 4H); 1.3 (m, 2H); 0.85 (m, 3H); MS: (M+) 670.2, 670.19;

4-Benzenesulfonyl-2-(2-benzenesulfonyl-ethyl)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-butyramide (Compound 4); ^{1}H-NMR (DMSO) δ: 8.61 (d, J=6Hz, 1H); 7.99 (d, J=8Hz, 1H); 7.91 (d, J=8Hz, 1H); 7.82 (m, 4H); 7.74 (m, 2H); 7.64 (m, 5H); 7.55 (t, J=8Hz, 1H); 5.21 (m, 1H); 3.3-3.0 (m, 5H); 1.8 (m, 1H); 1.6 (m, 5H); 1.3 (m, 2H); 0.86 (t, J=7Hz, 3H); MS: (M+) 597.2, 596.17;

(R)-*N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-2-cyclohexylmethyl-3-benzylsulfonyl-propionamide (Compound 5) ; ^{1}H NMR (DMSO): 8.96 (d, J=6Hz, 1H), 8.73 (d, J=6Hz, 1H), 7.99 (d, J=8H, 1H), 7.87 (m, 1H), 7.64 (m, 1H), 7.54 (m, 1H), 7.37

(m, 5H), 5.29 (m, 1H), 4.44 (s, 2H), 4.36 (s, 2H), 3.3-2.8 (m, 2H), 0.6-2.0 (m, 20H); MS: MH^+ 525.4 (524.23); and

N-[(S)-1-(1-Benzothiazol-2-yl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide (Compound 6); ^{1}H NMR: (DMSO), 8.79 (d, J=6.2Hz), 8.72 (d, J=6.2Hz), 1H], 8.30-8.22 (m, 2H), 7.71-7.61 (m, 2H), 7.43-7.33 (m, 5H), 5.46-5.33 (m, 1H), 4.53-4.38 (m, 2H), 3.57-3.30 (m, 10H), 3.13-3.02 (m, 1H), 2.66-2.54 (m, 2H), 2.04-1.90 (m, 1H), 1.83-1.68 (m, 1H), 0.97 (t, J=7.2Hz, 3H); MS: (M^++1) 558.

The method of Example 1 can also be modified by omitting the Oxone® oxidation step to prepare the following compounds:

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-cyclohexyl-2-cyclohexylmethyl-propionamide (Compound 7); ^{1}H NMR (DMSO): 8.50 (d, J=6Hz, 1H); 8.00 (d, J=8Hz, 1H); 7.89 (d, J=8Hz, 1H); 7.62 (t, J=7Hz, 1H); 7.53 (t, J=7Hz, 1H); 5.2(m, 1H); 2.0-0.8 (m, 35H); MS: M(H+) 453.2 (452.3);

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-isobutylsulfanyl-2-isobutylsulfanylmethyl-propionamide (Compound 8); ^{1}H NMR (DMSO): 8.73 (d, J=5Hz, 1H); 7.76 (d, J=7Hz, 1H); 7.87 (d, J=8Hz, 1H); 7.62 (dt, J=7,1Hz, 1H); 7.52 (dt, J=8,1Hz, 1H); 5.26 (m, 1H); 2.7 (m, 1H); 2.55 (m, 4H); 2.34 (d, J=7Hz, 2H); 2.29 (d, J=7Hz, 2H); 1.9 (m, 1H); 1.66 (m, 3H); 1.45 (m, 2H); 0.91 (t, J=6Hz, 3H), 0.90 (d, J=6Hz, 6H), 0.88 (d, J=3Hz, 3H), 0.84 (d, J=3Hz, 3H); MS: M(H+) 465.0 (464.22);

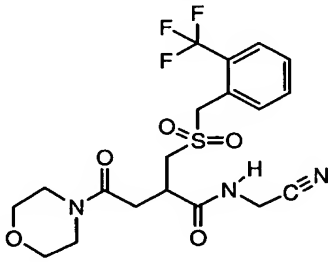
N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-benzylsulfanyl-2-benzylsulfanylmethyl-propionamide (Compound 9); ^{1}H NMR (DMSO): 8.80 (d, J=7Hz, 1H); 7.98 (d, J=8Hz, 1H); 7.88 (d, J=8Hz, 1H); 7.63 (t, J=7Hz, 1H); 7.53 (t, J=7Hz, 1H); 7.3-7.2 (m, 10H); 5.32 (m, 1H); 3.71 (s, 2H); 3.65 (d, J=3Hz, 2H); 2.87 (m, 1H); 2.45-2.3 (m, 4H); 2.0-1.4 (m, 4H); 0.92 (t, J=7Hz, 3H); MS: M(H+) 533.0 (532.19); and

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-4-phenylsulfanyl-2-(2-phenylsulfanyl-ethyl)-butyramide (Compound 10); ^{1}H NMR (DMSO): 8.73 (d, J=6Hz, 1H); 7.99 (d, J=8Hz, 1H); 7.88 (d, J=8Hz, 1H); 7.65 (t, J=8Hz, 1H); 7.53 (t, J=8Hz, 1H); 7.35-7.1 (m, 10H); 5.3 (m, 1H); 2.85 (m, 4H); 2.65 (m, 1H); 2.0-1.3 (m, 8H); 0.91 (t, J=7Hz, 3H); MS: M(H+) 533.0 (532.19).

EXAMPLE 2

N-Cyanomethyl-4-morpholin-4-yl-4-oxo-2-(2-trifluoromethyl-benzyl-sulfonylmethyl)-butyramide

(Compound 11)



A mixture comprised of 4-morpholin-4-yl-4-oxo-2-(2-trifluoromethyl-benzylsulfonylmethyl)-butyric acid (200mg, 0.47mmol), prepared as in reference 5, EDC (200mg, 1.05mmol), HOBt (200mg, 1.3mmol), and aminoacetonitrile hydrochloride (150mg, 1.6mmol) was treated with dichloromethyl (4mL) and 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (150mL), the solution was washed with water (30mL), saturated aqueous $NaHCO_3$ solution and brine, dried with magnesium sulfate and evaporated under vacuum. The product was crystallized from ethyl acetate/hexane to yield *N*-cyanomethyl-4-morpholin-4-yl-4-oxo-2-(2-trifluoromethyl-benzyl-sulfonylmethyl)-butyramide (156mg) as a yellowish solid; ^{1}H NMR: (DMSO) 8.87 (t, J=5.5Hz, 1H), 7.81-7.57 (m, 4H), 4.74 (d, J=14.5Hz, 1H), 4.67 (d, J=14.5Hz, 1H), 4.13 (d, J=5.5Hz, 2H), 3.63-3.26 (m, 11H), 2.75 (dd, J=6.4Hz, J=16.8Hz, 1H), 2.65 (dd, J=6.2Hz, J=16.8Hz, 1H); MS: (M^++1) 462;

The following compounds of Formula I were provided by proceeding as in Example 2:

N^4-(4-Carbamoyl-phenyl)-N^1-cyanomethyl-2-benzyl-sulfonylmethyl-succinamide (Compound 19); ^{1}H NMR: (DMSO) 10.24 (s, 1H), 8.93 (t, J=5.5Hz, 1H), 7.83 (s, 1H), 7.81 (d, J=8.4Hz, 2H), 7.60 (d, J=8.4Hz, 2H), 7.44-7.35 (m, 5H), 7.23 (s, 1H), 4.53 (d,

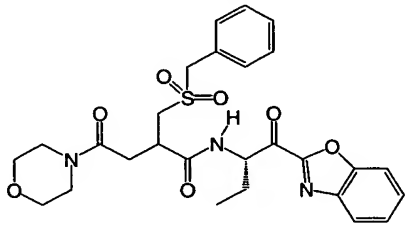
J=13.6Hz, 1H), 4.48 (d, J=13.6Hz, 1H), 4.14 (m, 2H), 3.50-3.30 (m, 2H), 3.20 (dd, J=4.7Hz, J=13.1Hz, 1H), 2.73 (d, J=6.7Hz, 2H); MS: (M^++1) 443; and

N-Cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl]-4-morpholin-4-yl-4-oxo-butyramide (Compound 25); ^{1}H NMR: (DMSO) 8.85 (t, J=5.5Hz, 1H), 7.52-7.43 (m, 2H), 7.31-7.22 (m, 2H), 7.13 (t, $J_{H,F}$=74Hz, 1H), 4.53 (s, 2H), 4.11 (d, J=5.5Hz, 2H), 3.58-3.20 (m, 11H), 2.72 (dd, J=6.7Hz, J=16.8Hz, 1H), 2.63 (dd, J=5.9Hz, J=16.8Hz, 1H); MS: (M^++1) 460;

EXAMPLE 3

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide

(Compound 29)



A mixture comprised of 4-Morpholin-4-yl-4-oxo-2-(benzyl-sulfonylmethyl)-butyric acid (300mg, 0.84mmol), EDC (250mg, 1.3mmol), HOBt (250mg, 1.6mmol) and (2S)-2-amino-1-benzooxazol-2-yl-butan-1-ol (250mg, 1.2mmol) was treated with dichloromethyl (4mL) followed by 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (150mL), the solution was washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$ solution and brine, dried with magnesium sulfate and evaporated under vacuum. The crude product was dissolved in dry dichloromethyl (10mL) and 1,1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (500mg, 1.2mmol) was added. After stirring at ambient temperature for 1 hour, the mixture was diluted with ethyl acetate (150mL) and treated with 0.26M $Na_2S_2O_3$ solution in saturated aqueous $NaHCO_3$. The organic phase was washed with saturated aqueous NaHCO3 and brine, dried with magnesium sulfate and

evaporated to yield N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide (377mg) as mixture of diastereomers. The product was purified by flash chromatography on silica gel (hexane/ethyl acetate ratio of 1:2 to 1:4); ^{1}H NMR: (DMSO), 8.85 (d, J=6.2Hz), 8.77 (d, J=6.2Hz), 1H],, 8.00 (d, J=7.7Hz), 7.99 (d, J=7.7Hz), 1H],, 7.90 (d, J=8.2Hz), 7.89 (d, J=8.2Hz), 1H], 7.64 (t, J=7.9Hz, 1H), 7.54 (t, J=7.4Hz, 1H), 7.42-7.34 (m, 5H), 5.25-5.12 (m, 1H), 4.55-4.38 (m, 2H), 3.60-3.28 (m, 10H), 3.12-3.02 (m, 1H), 2.64-2.50 (m, 2H), 2.08-1.91 (m, 1H), 1.82-1.65 (m, 1H), 0.98 (t, J=7.4Hz, 3H); MS: (M^++1) 542;

The following compounds of Formula I were provided by proceeding as in Example 3:

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-pentyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide (Compound 30); ^{1}H NMR: (DMSO), 8.84 (d, J=6.4Hz), 8.76 (d, J=6.4Hz), 1H],, 8.00 (d, J=7.7Hz), 7.98 (d, J=7.7Hz), 1H],, 7.89 (d, J=8.2Hz), 7.88 (d, J=8.2Hz), 1H], 7.64 (t, J=7.9Hz, 1H), 7.53 (t, J=7.4Hz, 1H), 7.42-7.34 (m, 5H), 5.30-5.17 (m, 1H), 4.53-4.37 (m, 2H), 3.56-3.26 (m, 10H), 3.12-3.00 (m, 1H), 2.66-2.52 (m, 2H), 2.00-1.86 (m, 1H), 1.76-1.61 (m, 1H), 1.48-1.22 (m, 4H), 0.85 (t, J=6.9Hz, 3H); MS: (M^++1) 570;

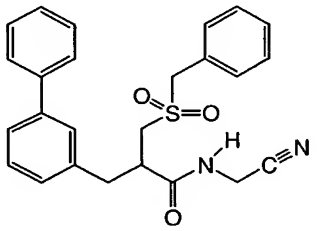
(S)-2,2-Difluoro-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butanoylamino)-3-oxo-hexanoic acid dimethylamide (Compound 31); ^{1}H NMR: (DMSO) 8.63-8.57 (m, 1H), 7.43-7.34 (m, 5H), 4.69-4.57 (m, 1H), 4.55-4.41 (m, 2H), 3.59-3.30 (m, 10H), 3.14-3.04 (m, 1H),, 2.98 (s), 2.96 (s), 3H],, 2.90 (s), 2.88 (s), 3H], 2.70-2.58 (m, 2H), 1.90-1.72 (m, 1H), 1.66-1.50 (m, 1H), 0.89 (t, J=6.9Hz, 3H); MS: (M^++1) 546; and

N-[(S)-1-(1-Benzylcarbamoyl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide (Compound 32); ^{1}H NMR: (DMSO) 9.26-9.19 (m, 1H),, 8.56 (d, J=6.7Hz), 8.51 (d, J=6.9Hz), 1H], 7.44-7.19 (m, 10H), 4.96-4.85 (m, 1H), 4.53-4.40 (m, 2H), 4.38-4.22 (m, 2H), 3.57-3.30 (m, 10H), 3.11-2.99 (m, 1H), 2.65-2.52 (m, 2H), 1.86-1.71 (m, 1H), 1.61-1.48 (m, 1H), 0.89 (t, J=7.2Hz, 3H); MS: (M^++1) 558.

EXAMPLE 5

3-Biphenyl-3-yl-*N*-cyanomethyl-2-benzylsulfonylmethyl-propionamide

(Compound 35)



3-Biphenyl-3-yl-2-benzylsulfonylmethyl-propionic acid (300mg, 0.76mmol), prepared as in Reference 9, was combined with EDC (300mg, 1.57mmol), HOBt (300mg, 1.96mmol), and aminoacetonitrile hydrochloride (150mg, 1.6mmol). Dichloromethyl (4mL) was added and then 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (150mL), the solution was washed with water (30mL), saturated aqueous $NaHCO_3$ solution and brine, dried with magnesium sulfate and evaporated under vacuum. The product, 3-biphenyl-3-yl-*N*-cyanomethyl-2-benzylsulfonylmethyl-propionamide (273mg), was crystallized from ethyl acetate/hexane as a white solid; ^{1}H NMR: (DMSO) 8.87 (t, J=5.5Hz, 1H), 7.68-7.14 (m, 14H), 4.45 (d, J=13.8Hz, 1H), 4.38 (d, J=13.8Hz, 1H), 4.13 (m, 2H), 3.49 (dd, J=9.4Hz, J=14.1Hz, 1H), 3.28-3.11 (m, 1H), 3.04-2.76 (m, 3H). MS: (M^++1) 433.

Proceeding as in Example 5 provided the following compound of Formula I:

3-Biphenyl-4-yl-*N*-cyanomethyl-2-benzylsulfonylmethyl-propionamide (Compound 36); ^{1}H NMR: (DMSO) 8.86 (t, J=5.5Hz, 1H), 7.65 (d, J=7.4Hz, 2H), 7.59 (d, J=7.4Hz, 2H), 7.47 (t, J=7.7Hz, 2H), 7.39-7.24 (m, 8H), 4.47 (d, J=13.8Hz, 1H), 4.40 (d, J=13.8Hz, 1H), 4.13 (m, 2H), 3.48 (dd, J=9.4Hz, J=14.1Hz, 1H), 3.23-3.11 (m, 1H), 3.04-2.75 (m, 3H). MS: (M^++1) 433; and

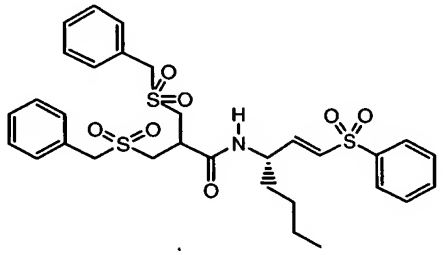
3-(3-Bromo-phenyl)-*N*-cyanomethyl-2-benzylsulfonylmethyl-propionamide (Compound 37); ^{1}H NMR: (DMSO) 8.84 (t, J=5.5Hz, 1H), 7.46-7.14 (m, 9H), 4.46 (d, J=13.8Hz, 1H), 4.40 (d, J=13.8Hz, 1H), 4.10 (m, 2H), 3.46 (dd, J=9.4Hz, J=14.1Hz, 1H),

3.18-3.07 (m, 1H), 2.97 (dd, J=14.1Hz, J=3.4Hz, 1H) 2.88-2.73 (m, 2H). MS: (M^++1) 435/437.

EXAMPLE 6

N-[(S)-1-((E)-2-Benzenesulfonyl-vinyl)-pentyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide

(Compound 38)



A mixture of 3-benzylsulfanyl-2-benzylsulfanylmethyl-propionic acid (161 mg), prepared as in Reference 1, 3-benzenesulfonyl-1-n-butylallylamine tosylate (212 mg), HOBt monohydrate (77 mg) and EDC (125 mg) in methylene chloride (6 mL) was treated with N-methylmorpholine (0.25 mL) and stirred at room temperature for 2.5 hours. The reaction mixture was poured into ice cold dilute hydrochloric acid. The product was extracted with ethyl acetate and the organic extracts were washed with aqueous sodium bicarbonate and then with saturated sodium chloride. After drying over magnesium sulfate the solvents were evaporated to give a residue which was crystallized from ethyl acetate/t-butylmethyl ether to yield *N*-[(S)-1-((E)-2-benzenesulfonyl-vinyl)-pentyl]-3-benzylsulfanyl-2-benzylsulfanylmethyl-propionamide (160 mg).

A solution of *N*-[(S)-1-((E)-2-benzenesulfonyl-vinyl)-pentyl]-3-benzylsulfanyl-2-benzylsulfanylmethyl-propionamide (50 mg) in methylene chloride (5 mL) was treated with m-chloroperbenzoic acid (108 mg) and then stirred at room temperature for 65 minutes. The reaction mixture was stirred with aqueous sodium bisulfite and sodium bicarbonate for 85 minutes and then extracted with methylene chloride. The organic extracts were washed with saturated aqueous sodium chloride and dried over magnesium

sulfate. Evaporation of the solvent gave a residue which was precipitated from ethyl acetate/t-butylmethyl ether to give *N*-[(S)-1-((E)-2-benzenesulfonyl-vinyl)-pentyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide (37 mg); ^{1}H NMR (DMSO): 8.61 (d, J=8Hz, 1H), 7.80 (d, J=7Hz, 2H), 7.69 (t, J=7H, 1H), 7.58 (t, J=8Hz, 2H), 7.38 (m, 10H), 6.86 (m, 2H), 4.6-4.3 (m, 5H), 3.5-3.4 (m, 5H), 1.5 (m, 2H), 1.2 (m, 4H), 0.8 (m, 3H); MS: MH^+ 632.2 (631.17).

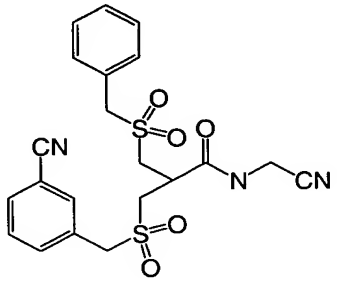
Proceeding as in Example 6 provided the following compound of Formula I:

N-(3-Benzenesulfonyl-1-phenethyl-allyl)-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide (Compound 39); ^{1}H NMR (DMSO): 8.75 (d, J=8Hz, 1H), 7.80 (d, J=7Hz, 2H), 7.70 (t, J=7H, 1H), 7.58 (t, J=8Hz, 2H), 7.4-7.1 (m, 15H), 6.9 (m, 2H), 4.6-4.2 (m, 5H), 3.6-3.3 (m, 5H), 2.6 (m, 2H), 1.8 (m, 2H); MS: MH^+ 680.4 (679.17);

EXAMPLE 7

N-Cyanomethyl-3-(3-cyano-benzylsulfonyl)-2-benzylsulfonyl-methyl-propionamide

(Compound 40)



A mixture of 3-acetylsulfanyl-2-benzylsulfanylmethyl-propionic acid (0.200g), prepared as in Reference 10, HOBt hydrate (0.13g), aminoacetonitrile hydrochloride (0.15g) and EDC (0.26g) was treated with methylene chloride (6 mL) and N-methylmorpholine (0.35 mL). After stirring for 80 minutes at room temperature, the reaction mixture was diluted with ethyl acetate (50mL) and washed sequentially with water, aqueous sodium bicarbonate and saturated aqueous sodium chloride. The solution was dried over magnesium sulfate and evaporated to give thioacetic acid *S*-[3-

benzylsulfanyl-2-(cyanomethyl-carbamoyl)-propyl] ester (0.218 g).

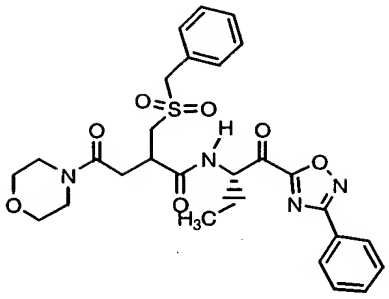
A solution of thioacetic acid *S*-[3-benzylsulfanyl-2-(cyanomethyl-carbamoyl)-propyl] ester (0.105 g) in dimethylformamide (1 mL) and water (0.8 mL) was cooled on ice and treated with 1 N aqueous potassium hydroxide (0.65 mL). 3-Cyanobenzylbromide (0.129 g) in dimethylformamide (0.8 mL) was added. The reaction mixture was allowed to warm to room temperature while stirring overnight. The reaction mixture was then poured into ice water and extracted with ethyl acetate (50 mL) and washed with water and saturated aqueous sodium chloride. The solution was dried over magnesium sulfate and evaporated to give 2-benzylsulfanylmethyl-3-(3-cyano-benzylsulfanyl)-*N*-cyanomethyl-propionamide (0.135 g).

2-Benzylsulfanylmethyl-3-(3-cyano-benzylsulfanyl)-*N*-cyanomethyl-propionamide (0.135 mg) in methanol (10mL) was treated with a solution of Oxone® (0.615g) in water (1.3mL) and the resulting mixture was stirred at room temperature for 45 minutes. The reaction mixture was diluted with water (50mL) and then the methanol was removed by rotary evaporation. The residue was diluted with ethyl acetate and water. The product was extracted with ethyl acetate and the organic layer washed with water and saturated aqueous sodium chloride. The solution was dried over magnesium sulfate and evaporated to give *N*-Cyanomethyl-3-(3-cyano-benzylsulfonyl)-2-benzylsulfonylmethyl-propionamide (0.138 g); ^{1}H NMR: (DMSO) 9.19 (t, J=5Hz, 1H), 7.88 (d, J=8Hz, 1H), 7.82 (s, 1H), 7.72 (d, J=9Hz, 1H), 7.62 (t, J=8Hz, 1H), 7.38 (s, 5H), 4.65 (d, J=14Hz, 1H), 4.58 (d, J=14Hz, 1H), 4.53 (d, J=13Hz, 1H), 4.47 (d, J=13Hz, 1H), 4.17 (d, J=5Hz, 2H), 3.5-3.3 (m, 5H); MS: (M^++1) 460.2; 459.09.

EXAMPLE 8

4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-{(S)-1-[1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methanoyl]-propyl}-butyramide

(Compound 41)

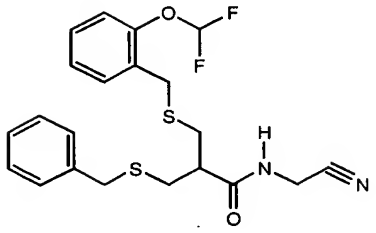


A mixture of (S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-one, prepared as in Reference 11, 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (200mg, 0.56mmol), EDC (200mg, 1.05mmol), HOBt (200mg, 1.30mmol), CH_2Cl_2 (4mL) and 4-methylmorpholine (0.5mL) was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (150mL), the solution was washed with water (30mL), saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$ and evaporated under vacuum. The crude product was dissolved in dry dichloromethyl (10mL) and 1,1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (500mg, 1.2mmol) was added. After stirring at ambient temperatures for 1 hour, the mixture was diluted with ethyl acetate (150mL) and treated with $Na_2S_2O_3$ solution (0.26M) in saturated aqueous $NaHCO_3$. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and evaporated. The product was purified by flash chromatography on silica gel (hexane/ethyl acetate in a 1:2 to 1:4 ratio) to yield 4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-{(S)-1-[1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methanoyl]-propyl}-butyramide (150mg) as mixture of diastereomers; ^{1}H NMR: (DMSO), 9.03 (d, J=5.9Hz), 8.89 (d, J=6.4Hz), 1H], 8.09-8.03 (m, 2H), 7.66-7.55 (m, 3H), 7.42-7.33 (m, 5H), 4.97-4.78 (m, 1H), 4.53-4.35 (m, 2H), 3.58-3.02 (m, 11H), 2.65-2.50 (m, 2H), 2.06-1.90 (m, 1H), 1.83-1.66 (m, 1H), 0.97 (t, J=7.2Hz, 3H); MS: (M^++1) 569.

Example 9

N-Cyanomethyl-2-[2-1,1-difluoro-methoxy)-benzylsulfanylmethyl]-3-benzylsulfanyl-propionamide

(Compound 42):



A mixture of 2-benzylsulfanylmethyl-3-[2-(1,1-difluoromethoxy)-benzyl-sulfanyl]-propionic acid (96 mg, 0.241 mmol)(prepared above in Reference 2), HOBt hydrate (37 mg, 0.24 mmol), aminoacetonitrile hydrochloride (33 mg, 0.36 mmol), EDC (69 mg, 0.36 mmol) and N-methylpyrolidinone (1 mL) was treated with N-methylmorpholine (0.050 mL) and then stirred at room temperature for 3 hours. The reaction mixture was then poured into cold dilute HCl and the product extracted with ethyl acetate, The organic extracts were washed with aqueous sodium bicarbonate then saturated sodium chloride and dried over magnesium sulfate. Evaporation of the solvent then gave N-cyanomethyl-2-[2-1,1-difluoro-methoxy)-benzylsulfanylmethyl]-3-benzylsulfanyl-propionamide (46 mg).

The following compounds of Formula 1 are provided by this method by substitution of 2-benzylsulfanylmethyl-3-[2-(1,1-difluoromethoxy)-benzylsulfanyl]-propionic acid with the appropriate carboxylic acid:

N-Cyanomethyl-3-(2-trifluoromethyl-benzylsulfanyl)-2-(2-trifluoro-methyl-benzylsulfanylmethyl)-propionamide (Compound 43); ^{1}H-NMR ($CDCl_3$) δ: 7.57 (m, 6H); 7.36 (t, J=7.4 Hz, 2H); 6.01 (m, 1H); 4.16 (d, J=5.9 Hz, 2H); 3.86 (s, 4H); 2.70 (m, 4H); 3.35 (m, 1H); MS: (M+) 507.0, M(-) 504.2;

N-Cyanomethyl-3-isobutylsulfanyl-2-isobutylsulfanylmethyl-propionamide (Compound 44); ^{1}H NMR (DMSO): 8.77 (t, J=6 Hz, 1H), 4.5 (d, J=6 Hz, 2H), 2.60 (s, 5H), 2.34 (d, J=7 Hz, 4H), 1.70 (hept, J=7 Hz, 2H), 0.91 (d, J=7Hz, 12H); MS: M(H+) 303.0 (302.15);

N-Cyanomethyl-4-phenylsulfanyl-2-(2-phenylsulfanyl-ethyl)-butyramide (Compound 45); ^{1}H NMR (DMSO): 8.83 (t, J=5Hz, 1H); 7.3 (m, 10H); 4.22 (d, J=6Hz, 2H); 2.90 (m, 4H); 2.65 (m, 1H); 1.85 (m, 2H); 1.72 (m, 2H); MS: M(H+) 370.4

(370.12);

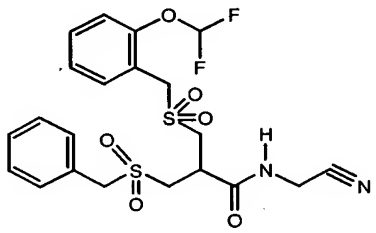
N-Cyanomethyl-3-[2-(1,1-difluoro-methoxy)-benzylsulfanyl]-2-[2-(1,1-difluoro-methoxy)-benzylsulfanylmethyl]-propionamide (Compound 46); ^{1}H NMR (DMSO): 8.88 (t, J=5Hz, 1H); 7.4-7.1 (m, 8H); 7.15 (t, J=74Hz, 2H); 4.18 (t,J=3Hz, 2H); 3.74 (d, J=13Hz, 4H); 2.75 (m, 1H); 2.65-2.5 (m, 4H); MS: M(H+) 504.1 (502.1); and

3-Benzylsulfanyl-2-benzylsulfanylmethyl-*N*-cyanomethyl-propionamide (Compound 47); ^{1}H NMR (DMSO): 8.86 (t, J=6Hz, 1H); 7.26 (m, 10H); 4.20 (d, J=5Hz, 2H); 3.7 (s, 4H); 2.73 (m, 1H); 2.55-2.37 (m, 4H); MS: M(H+) 370.4 (370.12).

Example 10

N-Cyanomethyl-2-[2-1,1-difluoro-methoxy)-benzylsulfonylmethyl]-3-benzylsulfonyl-propionamide

(Compound 48)



A solution of N-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzyl-sulfanylmethyl]-3-benzylsulfanyl-propionamide (46 mg) in methanol (5 mL) was treated with Oxone® (184 mg in 2.5 mL of water) and stirred at ambient temperature for 18 hours. An additional portion of Oxone® (166mg in 1.5 mL of water) was added along with more methanol (10 mL) and the reaction mixture was stirred again for 18 hours. Water was added to the reaction mixture and the methanol was removed by rotary evaporation and the product was extracted with ethyl acetate. The organic extracts were washed with aqueous sodium bicarbonate then saturated sodium chloride and dried over magnesium sulfate. Evaporation of the solvent then gave N-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl]-3-phenyl-methylsulfonyl-propionamide (67 mg); ^{1}H NMR (DMSO): 9.19 (t, J =5 Hz, 1H), 7.47 (m, 2H), 7.38 (s, 5H), 7.25 (m, 2H), 7.13 (t, J=74 Hz,

1H), 4.54 (s, 2H), 4.53 (d, J=14 Hz, 1H), 4.46 (d, J = 14 Hz, 1H), 4.16 (d, J = 5 Hz, 2H), 3.5 (m, 5H); MS: M(H+) 501.0 (500.09).

The following compounds of Formula 1 are provided by this method by substitution of N-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzyl-sulfanylmethyl]-3-benzylsulfanyl-propionamide with the appropriate N-cyanomethyl propionamide:

N-Cyanomethyl-3-(2-trifluoromethyl-benzylsulfonyl)-2-(2-trifluoromethyl-benzylsulfonylmethyl)-propionamide.(Compound 49); ^{1}H-NMR (DMSO) δ: 9.23 (t, J=5.4 Hz, 1H); 7.79 (m, 2H); 7.67 (m, 6H); 4.72 (m, 4H); 4.18 (t, J=2.7 Hz, 2H); 3.53-3.76 (m, 5H); MS: M(+) 539.0; M(-) 536.6;

4-Benzenesulfonyl-2-(2-benzenesulfonyl-ethyl)-*N*-cyanomethyl-butyramide (Compound 50); ^{1}H NMR (DMSO): 8.67 (t, J=5Hz, 1H); 7.85 (m, 4H); 7.73 (m, 2H); 7.64 (m, 4H); 4.06 (m, 2H); 3.12 (m, 4H); 2.4 (m, 1H); 1.66 (m, 4H); MS: M(H+) 435.2 (434.10);

N-Cyanomethyl-3-[2-(1,1-difluoro-methoxy)-benzylsulfonyl]-2-[2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl]-propionamide (Compound 51); ^{1}H NMR (DMSO): 9.17 (t, J=5Hz, 1H); 7.5-7.4 (m, 4H); 7.3-7.2 (m, 4H); 7.12 (t, J=74Hz, 2H); 4.54 (s, 4H); 4.15 (m, 2H); 3.6-3.4 (m, 5H); MS: M(H+) 567.2 (566.08); and

N-Cyanomethyl-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide (Compound 52); ^{1}H NMR (DMSO): 9.19 (t, J=5Hz, 1H); 7.38 (s, 10H); 4.53 (d, J=14Hz, 2H); 4.46 (d,J=14Hz, 2H); 4.17 (t, J=3Hz, 2H); 3.5-3.3 (m, 5H); MS: M(H+) 435.2 (434.1).

The following compounds of Formula I are provided by the methods described in this application:

N-[(S)-1-(1-Benzylcarbamoyl-methanoyl)-propyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide (Compound 53); ^{1}H-NMR (DMSO) δ: 9.27 (t, J=6Hz, 1H); 8.89 (d, J=6 Hz, 1H); 7.4-7.2 (m, 15H); 5 (m, 1H); 4.5 (m, 4H); 4.3 (m, 2H); 3.67 (m, 1H); 3.5-3.2 (m, 4H), 1.8 (m, 1H)1.6 (m, 1H); 0.91 (t, J=7Hz, 3H); MS: (M+) 599.0, M(-) 598.18;

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-2-[2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl]-3-benzylsulfonyl-propionamide (Compound 54); ^{1}H-NMR (DMSO) δ: 9.1 (t, J=6Hz, 1H); 7.99 (d, J=8Hz, 1H); 7.88 (d, J=8Hz, 1H); 7.7-7.2 (m, 14H); 5.35 (m, 1H); 4.6-4.4 (m, 5H); 3.7-3.3 (m, 5H); 1.9 (m, 1H), 1.7 (m, 1H)1.45 (m, 2H); 0.90 (t, J=7Hz, 3H); MS: (M+) 599.0, M(-) 598.18;

N-Cyanomethyl-3-(2-methyl-propane-1-sulfonyl)-2-(2-methyl-propane-1-sulfonylmethyl)-propionamide (Compound 55); ^{1}H-NMR (DMSO) δ: 9.13 (t, J=5Hz, 1H); 4.14 (m, 2H); 3.5-3.3 (m, 5H), 3.1-2.95 (m, 4H), 2.17 (h, J=7Hz, 2H)1.01 (d, J=7Hz, 12H); MS: (M+) 367.0, 366.13;

Acetic acid (2S,3S)-3-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butanoylamino)-4-oxo-azetidin-2-yl ester (Compound 58); ^{1}H NMR: (DMSO) 9.19 (d, J=5.9Hz, 1H),, 8.94 (d, J=7.6Hz), 8.90 (d, J=7.6Hz), 1H], 7.42-7.35 (m, 5H), 5.70 (m, 1H), 4.60 (m, 1H), 4.56-4.40 (m, 2H), 3.58-3.06 (m, 11H), 2.70-2.50 (m, 2H), 2.07 (s, 3H); MS: (M^++1) 482;

N-Cyanomethyl-3-(2-methyl-thiazol-4-ylmethylsulfonyl)-2-benzyl-sulfonylmethyl-propionamide (Compound 59); ^{1}H NMR (DMSO): 9.14 (t, J=5 Hz, 1H), 7.52 (s, 1H), 7.38 (s, 5H), 4.64 (s, 2H), 4.53 (d, J=14 Hz, 1H), 4.46 (d, J = 14 Hz, 1H), 4.16 (d, J = 5 Hz, 2H), 3.5 (m, 5H), 2.63 (s, 3H); M=455.06, M(H+)=456.0;

N-(3-Benzenesulfonylamino-2-oxo-propyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide (Compound 60); ^{1}H NMR: (DMSO) 8.46 (t, J=5.2Hz, 1H), 7.97 (t, J=5.7Hz, 1H), 7.79 (d, J=7Hz, 2H), 7.66-7.52 (m, 3H), 7.44-7.36 (m, 5H), 4.56-4.43 (m, 2H), 3.94 (d, J=5.2Hz, 2H), 3.84 (d, J=5.7Hz, 2H), 3.59-3.04 (m, 11H), 2.75-2.55 (m, 2H); MS: (M^++1) 566;

3-Biphenyl-3-yl-*N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzyl-sulfonylmethyl]-propionamide (Compound 61); ^{1}H NMR: (DMSO) 8.86 (t, J = 5.4 Hz, 1H), 7.70-7.10 (m, 13H), 7.12 (t, J = 73.7 Hz, 1H), 4.46 (s, 2H), 4.13 (m, 2H), 4.10 (d, J = 5.6Hz, 2H), 3.57 (m, 1H), 3.20-3.00 (m, 2H), 3.00-2.80 (m, 2H); MS: (M^++1) 499;

(3'-{2-(Cyanomethyl-carbamoyl)-3-[2-(1,1-difluoro-methoxy)-benzyl-sulfonyl]-propyl}-biphenyl-4-yl)-carbamic acid ethyl ester (Compound 62); ^{1}H NMR: (DMSO) 9.70 (s, 1H), 8.84 (t, J = 5.4 Hz, 1H), 7.55 (s, 4H), 7.50-7.15 (m, 8H), 7.11 (t, J = 73.7 Hz, 1H),

4.45 (s, 2H), 4.13 (m, 2H), 4.09 (d, J = 5.5Hz, 2H), 3.56 (m, 1H), 3.20-3.00 (m, 2H), 2.95-2.75 (m, 2H), 1.24 (t, J = 6.9 Hz, 3H); MS: (M^++1) 586;

N-Cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl]-3-(4'-methylsulfonylamino-biphenyl-3-yl)-propionamide (Compound 63); ^{1}H NMR: (DMSO) 9.77 (s, 1H), 8.79 (t, J = 5.4 Hz, 1H), 7.57 (d, J=8.6, 2H), 7.50-7.00 (m, 8H), 7.27 (d, J=8.6 Hz, 2H), 7.06 (t, J = 73 Hz, 1H), 4.40 (s, 2H), 4.04 (d, J = 5.6Hz, 2H), 3.51 (m, 1H), 3.20-3.00 (m, 2H), 2.90-2.70 (m, 2H); MS: (M^++1) 592;

3-(3-Bromo-phenyl)-*N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-phenyl-methylsulfonylmethyl]-propionamide (Compound 64); ^{1}H NMR: (DMSO) 8.80 (t, J = 5.4 Hz, 1H), 7.50-7.35 (m, 4H), 7.35-7.15 (m, 4H), 7.13 (t, J = 73 Hz, 1H), 4.46 (s, 2H), 4.06 (d, J = 5.4Hz, 2H), 3.53 (m, 1H), 3.20-3.00 (m, 2H), 2.90-2.70 (m, 2H); MS: (M^++1) 501;

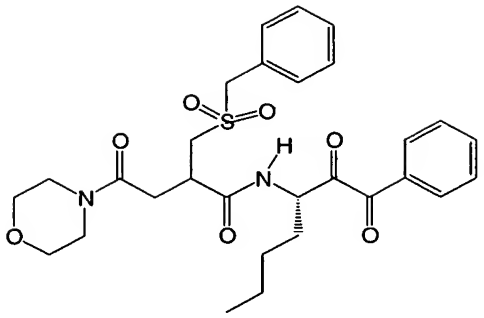
N-Cyanomethyl-2-((E)-3-phenyl-allyl)-3-benzylsulfonyl-propionamide (Compound 65); ^{1}H NMR: (DMSO) 8.85 (t, J = 5.4 Hz, 1H), 7.40-7.10 (m, 10H), 6.35 (d, J=15 Hz, 1H), 6.15-5.95 (m, 1H), 4.41 (s, 2H), 4.08 (d, J = 5.4Hz, 2H), 3.56-3.35 (m, 2H), 3.25-2.90 (m, 3H); MS: (M^++1) 383; and

N-Cyanomethyl-3-benzylsulfonyl-2-(3-phenyl-propyl)-propionamide (Compound 66); ^{1}H NMR: (DMSO) 8.91 (t, J = 5.4 Hz, 1H), 7.45-7.10 (m, 10H), 4.41 (s, 2H), 4.08 (d, J = 5.4Hz, 2H), 3.30-2.80 (m, 3H), 2.34 (t, J = 7.4 Hz, 2H), 2.22-2.12 (m, 2H), 2.10-1.85 (m, 2H); MS: (M^++1) 385.

EXAMPLE 11

4-Morpholin-4-yl-4-oxo-*N*-[1-(2-oxo-2-phenyl-acetyl)-pentyl]-2-benzylsulfonylmethyl-butyramide

(Compound 67)



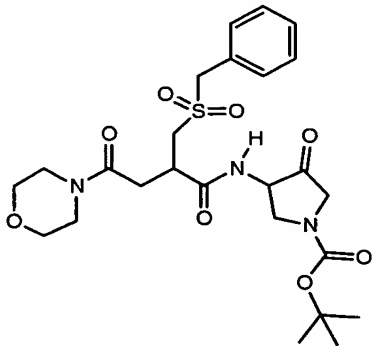
2-Amino-1-(2-phenyl-[1,3]dithian-2-yl)-hexan-1-ol, prepared as in reference 12, was coupled with 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid, according to the procedure outlined in example 8, resulting in *N*-{1-[Hydroxy-(2-phenyl-[1,3]dithian-2-yl)-methyl]-pentyl}-4-morpholin-4-yl-4-oxo-2-benzylsulfonyl-methyl-butyramide as a mixture of diastereomers.

N-{1-[Hydroxy-(2-phenyl-[1,3]dithian-2-yl)-methyl]-pentyl}-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide (0.23 g, 0.35 mmol) in 9mL acetonitrile and 2.25mL water at 23°C was mixed with finely ground $HgCl_2$ (212 mg, 0.78 mmol) and finely ground calcium carbonate (90 mg, 0.89 mmol). The mixture was stirred for 25 minutes and then diluted with ethyl acetate. Water was added and the pH lowered to 6 by the addition of 1N HCl. After separation, the organic layer was washed sequentially with water and brine (twice). The organics were dried with magnesium sulfate, concentrated and chromatographed on silica gel using a hexane-ethyl acetate gradient to afford 150 mg of *N*-[1-(1-Hydroxy-2-oxo-2-phenyl-ethyl)-pentyl]-4-morpholin-4-yl-4-oxo-2-phenyl-methylsulfonylmethyl-butyramide as a mixture of diastereomers (76% yield).

N-[1-(1-Hydroxy-2-oxo-2-phenyl-ethyl)-pentyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide was oxidized by methods described in the above examples resulting in 4-morpholin-4-yl-4-oxo-*N*-[1-(oxo-phenyl-acetyl)-pentyl]-2-benzylsulfonylmethyl-butyramide as a mixture of diastereomers; ^{1}HNMR: (DMSO), 8.9 (d, J = 6 Hz), 1/2H diastereomeric],, 8.86 (d, J = 6 Hz), 1/2H diastereomeric], 7.89-7.84 (m, 2H), 7.7-7.67 (m, 1H), 7.56-7.5 (m, 2H), 7.4-7.3 (m, 5H), 4.56-4.54 (m, 1H), 4.41-4.35 (m, 2H), 3.4-4.6 (m, 4H), 3.35-3.25 (m, 4H), 3.2-3.1 (m, 2H), 2.99 –2.95 (m, 1H), 1.9-1.6 (m, 2H), 1.5-1.2 (m, 6H), 1.0-0.9 (m, 3H); MS: (M^+ + 1) 557.

EXAMPLE 12

3-(4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-4-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester



(Compound 68)

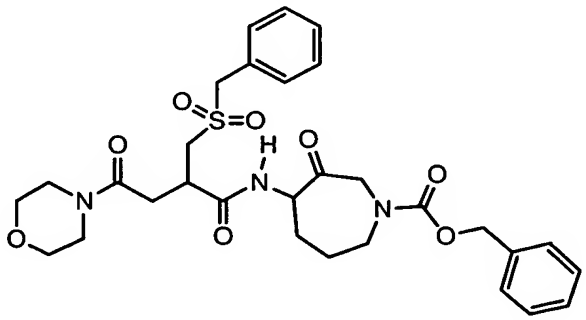
4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (120mg, 0.34mmol), 3-amino-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (150mg, 0.74mmol), prepared as in reference 13, EDC (0.3g, 1.6mmol), and HOBt (150mg, 0.96mmol) were combined. Dichloromethyl (10mL) was added and then 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2hours. After dilution with ethyl acetate (200mL) the solution was washed with 1N aqueous HCl (50mL), saturated aqueous $NaHCO_3$ (50mL) and brine (50mL), dried with $MgSO_4$ and evaporated under vacuum. The crude 3-hydroxy-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester was dissolved in DMSO (5mL). Triethylamine (0.5mL) and then SO_3 pyridine complex (150mg) were added and the mixture was stirred at ambient temperature for 3 hours. After dilution with ethyl acetate (100mL), the solution was washed with water (50mL) and brine, dried with $MgSO_4$ and evaporated under vacuum. The residue was purified by flash chromatography on silica gel. Eluent: 5% methanol in ethyl acetate. Yield: 40mg 3-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-4-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester as white solid as mixture of diastereomers; ^1H NMR: (DMSO) 8.80-8.66 (m, 1H), 7.42-

7.34 (m, 5H), 4.52-4.41 (m, 2H), 4.34-4.20 (m, 1H), 3.98-3.88 (m, 1H), 3.82 (d, J=18.5Hz, 1H), 3.70-3.05 (m, 13H), 2.70-2.52 (m, 2H), 1.41 (s, 9H); MS: $(M+H)^+$ 538.

EXAMPLE 13

4-(4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-3-oxo-azepane-1-carboxylic acid benzyl ester

(Compound 69)



Sodium hydride (60% in mineral oil, 10g, 250mmol) was suspended in dry DMF. Allyl-carbamic acid benzyl ester (19.1g, 100mmol) was added drop wise at ambient temperature. After stirring for 5 minutes, 5-bromo-1-pentene (25g, 168mmol) was added drop wise. Stirring was continued at 50°C for 1 hour. The reaction was quenched with water and then partitioned between diethyl ether and water. The ether layer was washed with water and brine, dried with $MgSO_4$ and evaporated under vacuum. Flash chromatography (ethyl acetate/hexane 1:9) gave 15.5g allyl-pent-4-enyl-carbamic acid benzyl ester.

Allyl-pent-4-enyl-carbamic acid benzyl ester (15.5g, 59.8mmol) was dissolved in dichloromethyl and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (1g) was added. The mixture was refluxed under a nitrogen atmosphere until TLC analysis showed complete reaction. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (ethyl acetate/hexane 1:9). Yield: 7.8g 2,3,4,7-Tetrahydro-azepine-1-carboxylic acid benzyl ester.

To a solution of 2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (4.5g, 19.45mmol) in dichloromethyl (50mL) was added m-chloroperbenzoic acid (60mmol).

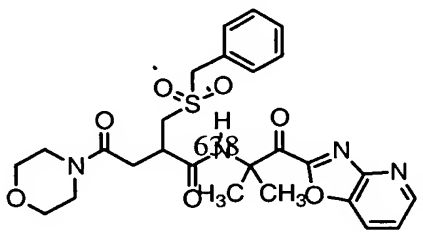
The mixture was stirred at ambient temperature for 16 hours. Saturated aqueous K_2CO_3 solution was added and the mixture was extracted with dichloromethyl. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and evaporated under vacuum. The crude epoxide was dissolved in a 8:1 methanol/water mixture (100mL). Ammonium chloride (3.2g, 60mmol) and sodium azide (3.9g, 60mmol) was added and the mixture was heated at 60°C for 48 hours. Most of the solvent was removed under vacuum. The residue was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (200mL) and brine (200mL), dried with $MgSO_4$ and evaporated under vacuum. Flash chromatography of the residue (hexane/ethyl acetate 3:1) gave 3.3g of 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester.

To a solution of 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester (3.3g, 11.37mmol) in methanol (50mL) was added triethylamine (5mL) and 1,3-propanedithiol (3.42mL, 35mmol). The mixture was stirred at ambient temperature until TLC analysis showed complete consumption of the starting material. A white precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was triturated with a 1:1 hexane/diethyl ether mixture to remove excess dithiol and dried under vacuum.

The crude 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester was coupled to 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid and oxidized, as described above, to yield 4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-3-oxo-azepane-1-carboxylic acid benzyl ester; ^{1}H NMR: (DMSO) 8.46-8.42 (m, 1H), 7.44-7.24 (m, 10H), 5.18-5.04 (m, 2H), 4.52-4.33 (m, 4H), 4.04-3.76 (m, 2H), 3.58-3.30 (m, 11H), 3.11-3.03 (m, 1H), 2.96-2.78 (m, 1H), 2.72-2.57 (m, 1H), 1.84-1.55 (m, 4H); MS: $(M+H)^+$ 600.

EXAMPLE 14

N-(1,1-Dimethyl-2-oxazolo[4,5-b]pyridin-2-yl-2-oxo-ethyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide



(Compound 70)

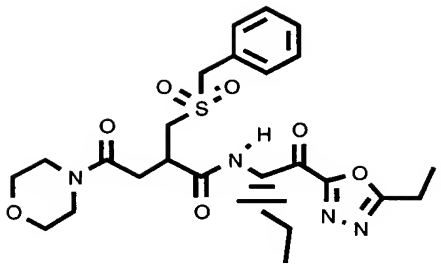
To a stirred mixture of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (142mg, 0.4mmol), 2-amino-2-methyl-1-oxazolo[4,5-b]pyridin-2-yl-propan-1-one TFA salt (165mg), prepared as in reference 14, and HOBt (73mg, 0.45mmol) in $MeCl_2$ (5ml) was added EDC (115mg, 0.6mmol) and N-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography to yield 92 mg of *N*-{1-[(5-Ethyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-butyl}-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide.

This amide was treated with Dess-Martin periodinane (125.6mg, 0.254mmol) at room temperature. After stirring for 1 hour, 5ml of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 31 mg of *N*-(1,1-dimethyl-2-oxazolo[4,5-b]pyridin-2-yl-2-oxo-ethyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; H^1 NMR(DMSO-d): 9.36(1H, s, NH), 8.68(1H, d, J=4.7Hz), 8.34(1H, d, J=8.42Hz), 7.62(1H, dd, J=4.7Hz, J=8.42Hz), 7.4-7.4(5H, m), 4.41-4.3(2H, s), 3.5-3(12H, m), 2.2-2.1(1H, m), 1.6(3H, s), 1.51(3H, s); MS: 541.4(M-1), 543.4(M+1).

EXAMPLE 15

N-[1-(5-Ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide

(Compound 71)

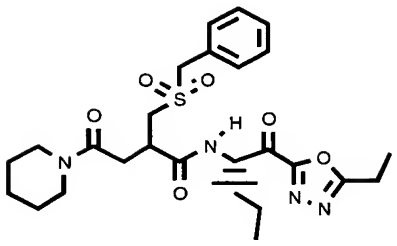


To a stirred mixture of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (177.7mg, 0.5mmol), 2-amino-1-(5-ethyl-1,3,4-oxadiazole-2-yl)-1-pentanol HCl salt (117.5mg), and HOBt (91.8mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and N-methylmorpholine (0.3ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 240 mg of crude product (MS: 536(M-1), 538.4(M+1)). Without further purification, the crude product was treated with Dess-Martin periodinane (334mg, 0.67mmol) at room temperature in 5mL of $MeCl_2$. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 110 mg of *N*-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; H^1 NMR(DMSO-d): 8.84(1/2H, d, NH, diastereomeric), 8.78(1/1H, d, NH, diastereomeric), 7.45-7.2(5H, m), 5.05-4.9(1H, m), 4.48-4.3(2H,m), 3.6-3.4(4H, m), 3.4-3.2(4H, m), 3.1-2.4(6H, m), 1.9-1.75(1H, m), 1.7-1.55(2H, m), 1.25-1.2(2H, m), 1.2-1.1(3H, m), 0.9-0.8(3H, m); MS: 534M-1), 535.8(M+1).

EXAMPLE 16

N-[1-(5-Ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-oxo-2-benzylsulfonyl-methyl-4-piperidin-1-yl-butyramide

(Compound 72)



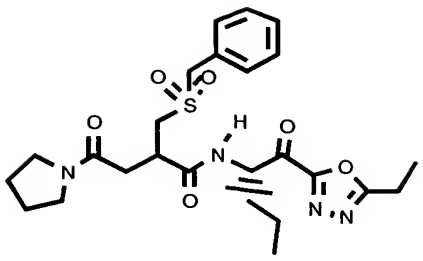
To a stirred mixture 4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyric acid (176.5mg, 0.5mmol), 2-amino-1-(5-ethyl-1,3,4-oxadiazole-2-yl)-1-pentanol HCl salt (117.5mg), and HOBt (91.8mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and N-methylmorpholine (0.3ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 270mg of crude product; MS: 534.1(M-1), 535.7(M+1).

The amide was then treated with Dess-Martin periodinane (378.7mg, 0.675mmol) at room temperature in 5 ml of $MeCl_2$. After stirring for 1 hour, 5ml of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 165 mg of *N*-[1-(5-Ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-oxo-2-benzyl-sulfonyl-methyl-4-piperidin-1-yl-butyramide; H^1 NMR (DMSO-d): 8.85(1/2H, d, NH, diastereomeric), 8.78(1/2, d, NH, diastereomeric), 7.4-7.2(5H, m), 5.1-4.9(1H, m), 4.5-4.3(2H,m), 3.5-3.2(8H, m), 3.1-2.6(1H, m), 2.9(2H, m), 1.9-1.6(2H, m), 1.6-1.2(8H, m), 1.24(3H, m), 0.9-0.8(3H, m); MS: 531.6(M-1), 533.4(M+1).

EXAMPLE 17

N-[1-(5-Ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-oxo-2-benzylsulfonyl-methyl-4-pyrrolidin-1-yl-butyramide

(Compound 73)

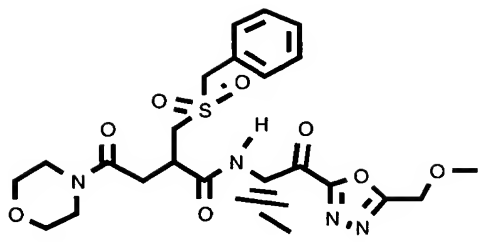


To a stirred mixture 4-cyclopentyl-4-oxo-2-benzylsulfonylmethyl-butyric acid (169.5mg, 0.5mmol), 2-amino-1-(5-ethyl-1,3,4-oxadiazole-2-yl)-1-pentanol HCl salt (117.5mg), and HOBt (91.8mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and N-methylmorpholine (0.3ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 240 mg of crude product. The crude product was treated with Dess-Martin periodinane (343mg, 0.693mmol) at room temperature in 5mls of $MeCl_2$. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 145 mg of *N*-[1-(5-Ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-oxo-2-benzylsulfonyl-methyl-4-pyrrolidin-1-yl-butyramide; H^1 NMR(DMSO-d): 8.85(1/2H, d, NH, diastereomeric), 8.78(1/2H, d, NH, diastereomeric), 7.5-7.3(5H, m), 5.1-4.95(1H, m), 4.5-4.3(2H,m), 3.5-3.2(8H, m), 3.2-3(1H, m), 2.82(2H, m), 2-1.8(6H, m), 1.6-1.3(2H, m), 1.24(3H, m), 0.9-0.8(3H, m); MS: 518.2(M-1), 519.7(M+1).

EXAMPLE 18

N-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide

(Compound 74)



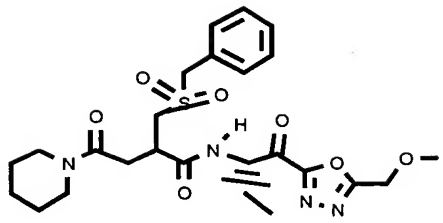
To a stirred mixture of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (230mg, 0.65mmol), 2-amino-1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-butan-1-one TFA salt (204mg), prepared as in reference 15, and HOBt (119mg, 0.78mmol) in $MeCl_2$ (5ml), was added EDC (187mg, 0.98mmol) and N-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 82mg of *N*-{1-[Hydroxy-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-morpholin-4-yl-4-oxo-2-benzylsulfonyl-methyl-butyramide; MS: 537.6(M-1), 539.8(M+1).

This amide then was treated with Dess-Martin periodinane (111mg, 0.149mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ was added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 13mgs of <u>*N*-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonyl-methyl-butyramide</u>; H^1 NMR($CDCl_3$): 7.8, 7.5(1H, d,d NH, diastereomeric), 7.4-7.2(5H, m), 5.3-5.1(1H, m), 4.6(2H, s, OCH_2), 4.3-4.1(3H, m), 3.8-3.1(13H, m), 3-2.4(2H, m), 2.2-1.5(2H, m), 0.95(3H, t); MS: 535.7(M-1), 537.5(M+1).

EXAMPLE 19

<u>*N*-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide</u>

(Compound 75)



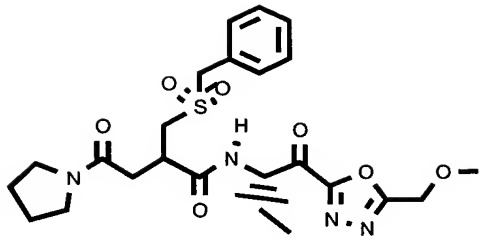
To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyric acid (229mg, 0.65mmol), 2-amino-1-(5-methoxymethyl-1,3,4-oxadiazole-2-yl)-1-propanol TFA salt (204mg), prepared as in reference 15, and HOBt (119mg, 0.78mmol) in $MeCl_2$ (5ml), was added EDC (187mg, 0.98mmol) and N-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 130 mg of *N*-{1-[hydroxy-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide; MS: 535.4(M-1), 537.7(M+1).

The amide then was treated with Dess-Martin periodinane (180mg, 0.364mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 26mgs of <u>*N*-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide</u>; H^1 NMR($CDCl_3$): 8, 7.7(1H, d,d, NH, diastereomeric), 7.4-7.2(5H, m), 5.3-5.1(1H, m), 4.6(2H, s, OCH_2), 4.3-4.1(3H, m), 3.8-3.2(9H, m), 3-2.4(2H, m), 2.2-1.4(8H, m), 0.95(3H, t); MS: 535.7(M+1).

EXAMPLE 20

<u>*N*-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide</u>

(Compound 76)



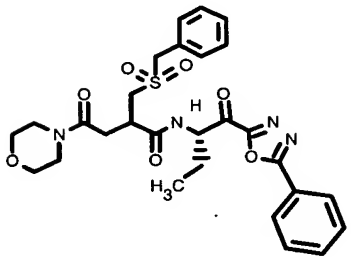
To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyric acid (220mg, 0.65mmol), 2-amino-1-(5-methoxymethyl-1,3,4-oxadiazole-2-yl)-1-propanol TFA salt (204mg), prepared as in reference 15, and HOBt (119mg, 0.78mmol) in $MeCl_2$ (5ml), was added EDC (187mg, 0.98mmol) and *N*-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 84 mg of *N*-{1-[Hydroxy-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide. Without further purification, the crude product was used for next reaction; MS: 521.6(M-1), 523.2(M+1).

This amide was treated with Dess-Martin periodinane (114mg, 0.153mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 17 mg of <u>*N*-[1-(5-Methoxymethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide</u>; H^1 NMR($CDCl_3$): 8.2, 8(1H, d,d, NH, diastereomeric), 7.6-7.2(5H, m), 5.3-5.1(1H, m), 4.6(2H, s, OCH_2), 4.3-4.1(3H, m), 3.8-3.2(9H, m), 3-2.4(2H, m), 2.2-1.4(6H, m), 0.95(3H, t); MS:519.6(M-1), 521.6(M+1).

EXAMPLE 21

<u>4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide</u>

(Compound 77)



To a stirred mixture of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (177mg, 0.5mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-butanol TFA salt (175mg), prepared as in reference 16, and HOBt (92mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and *N*-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 308 mg of *N*-{1-[Hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide. Without further purification, the crude product was used for next reaction; MS: 569.6(M-1), 571.4(M+1).

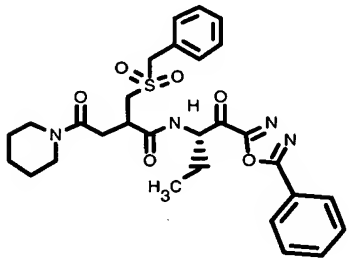
This amide was treated with Dess-Martin periodinane (371mg, 0.75mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 224 mg of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; H^1 NMR(DMSO-d): 8.9, 8.84 (1H, d, d, NH, diastereomeric), 8.1-8(2H, m), 7.7-7.6(3H, m), 7.4-7.3(5H, m),5.1-4.9(1H, m), 4.5-4.3(2H, m), 3.6-3.3(11H, m), 3.12-3(1H, m), 2.65-2.5(1H, m) , 2-1.9(1H, m), 1.8-1.7(1H, m), 0.96(3H, t); MS: 567.6(M-1), 569.4(M+1).

EXAMPLE 22

4-Oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-

4-piperidin-1-yl-butyramide

(Compound 78)



To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyric acid (177mg, 0.5mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-butanol TFA salt (175mg) , prepared as in reference 16, and HOBt (92mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and *N*-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 284 mg of *N*-{1-[Hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-oxo-2-henylmethylsulfonylmethyl-4-piperidin-1-yl-butyramide. Without further purification, the crude product was used for next reaction; MS: 567.6(M-1), 569.6(M+1).

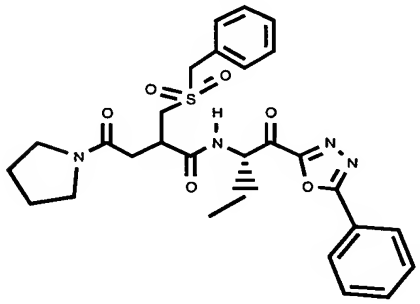
This amide was treated with Dess-Martin periodinane (371mg, 0.75mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 237 mg of 4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-piperidin-1-yl-butyramide; H^1 NMR (DMSO-d): 8.9, 8.84 (1H, d, d, NH, diastereomeric), 8.1-8(2H, m), 7.7-7.6(3H, m), 7.4-7.3(5H, m),5.1-4.9(1H, m), 4.5-4.3(2H, m), 3.4-3.1(7H, m), 3.12-3(1H, m), 2.65-2.5(1H, m) , 2-1.9(1H, m), 1.8-1.7(1H, m), 1.6-1.2(6H, m), 0.96(3H, t); MS: 565.4(M-1), 567.6(M+1).

EXAMPLE 23

4-Oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-

propyl]-4-pyrrolidin-1-yl-butyramide

(Compound 79)



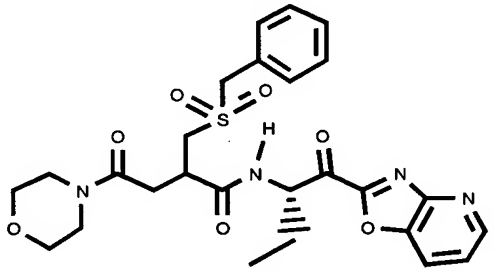
To a stirred mixture of 4-Oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyric acid (170mg, 0.5mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-butanol TFA salt (175mg) , prepared as above, and HOBt (92mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and *N*-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 280 mg of *N*-{1-[Hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-oxo-2-henylmethylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide. Without further purification, the crude product was used for next reaction; MS: 553.6(M-1), 555.4(M+1).

This amide was treated with Dess-Martin periodinane (371mg, 0.75mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 200mg of 4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-pyrrolidin-1-yl-butyramide; H^1 NMR (DMSO-d): 8.9, 8.84 (1H, d, d, NH, diastereomeric), 8.1-8(2H, m), 7.7-7.6(3H, m), 7.4-7.3(5H, m),5.1-4.9(1H, m), 4.5-4.3(2H, m), 3.4-3.1(7H, m), 3.12-3(1H, m), 2.65-2.5(1H, m) , 2.1-1.6(6H, m), 0.96(3H, t); MS: 551.6(M-1), 553.6(M+1).

EXAMPLE 24

4-Morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-butyramide

(Compound 80)



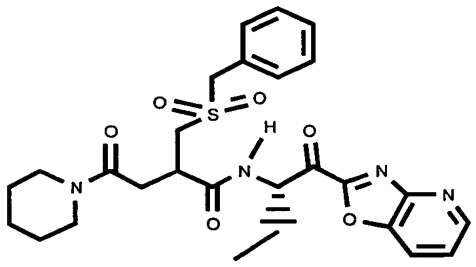
To a stirred mixture of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (177mg, 0.5mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-butanol TFA salt (175mg), prepared as in reference 17, and HOBt (92mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and *N*-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 308 mg of *N*-[1-(Hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; MS: 543.6 (M-1), 545.6(M+1)

This amide was treated with Dess-Martin periodinane (371mg, 0.75mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 224 mg of 4-morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-butyramide; H^1 NMR (DMSO-d): 8.96, 8.85(1H, d,d, NH, diastereomeric), 8.75-8.7(1H, m), 8.42-8.3(1H, m), 7.7-7.6(1H, m), 7.4-7.3(5H, m), 5.15-5.04(1H, m), 4.5-4.3(2H, m), 3.6-3.2(11H, m), 3.15-3.0(1H, m), 2.7-2.5(1H, m), 2.1-1.9(1H, m), 1.8-1.7(1H, m), 0.98(3H, t); MS: 541.2(M-1), 543.2(M+1).

EXAMPLE 25

N-[1-(Oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonyl-methyl-4-piperidin-1-yl-butyramide

(Compound 81)



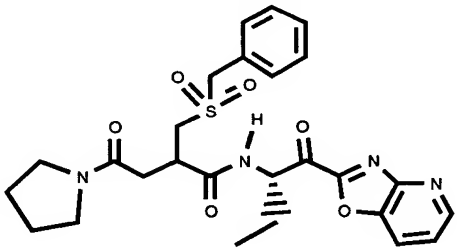
To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyric acid (177mg, 0.5mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-butanol TFA salt (175mg) , prepared as in reference 17, and HOBt (92mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and N-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 284 mg of *N*-[1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-4-oxo-2-henylmethylsulfonylmethyl-4-piperidin-1-yl-butyramide; MS: 541.6 (M-1), 543.4(M+1).

This amide was treated with Dess-Martin periodinane (371mg, 0.75mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 237 mg of *N*-[1-(Oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonyl-methyl-4-piperidin-1-yl-butyramide; H^1 NMR DMSO-d): 8.93, 8.83(1H, d,d, NH, diastereomeric), 8.75-8.72(1H, m), 8.4-8.37(1H, m), 7.7-7.6(1H, m), 7.4-7.3(5H, m), 5.15-5(1H, m), 4.5-4.3(2H, m), 3.45-3.2(9H, m), 3.1-3(1H, m), 2.67-2.5(1H, m), 2.1-1.9(1H, m), 1.84-1.7(1H, m), 1.6-1.5(2H, m), 1.5-1.3(4H, m), 0.98(3H, t); MS: 539.4(M-1), 541.2(M+1).

EXAMPLE 26

N-[1-(Oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonyl-methyl-4-pyrrolidin-1-yl-butyramide

(Compound 82)



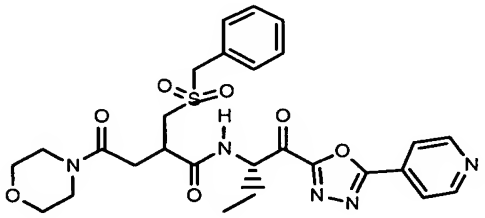
To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyric acid (170mg, 0.5mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-butanol TFA salt (175mg) , prepared as in reference 17, and HOBt (92mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and *N*-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 280 mg of *N*-[1-(Hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-4-oxo-2-henylmethylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide. Without further purification, the crude product was used for next reaction; MS: 527.6(M-1), 529.4(M+1).

This amide was treated with Dess-Martin periodinane (371mg, 0.75mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 200mg of *N*-[1-(Oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonyl-methyl-4-pyrrolidin-1-yl-butyramide; H^1 NMR (DMSO-d): 8.96, 8.87(1H, d,d, NH, diastereomeric), 8.75-8.72(1H, m), 8.45-8.3(1H, m), 7.7-7.6(1H, m), 7.45-7.3(5H, m), 5.2-5(1H, m), 4.5-4.3(2H, m), 3.5-3.15(7H, m), 3.15-3(1H, m), 2.55-2.4(1H, m), 2.1-1.95(1H, m), 1.9-1.6(5H, m), 0.98(3H, t); MS: 525.2(M-1), 526.8(M+1).

EXAMPLE 27

4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide

(Compound 83)



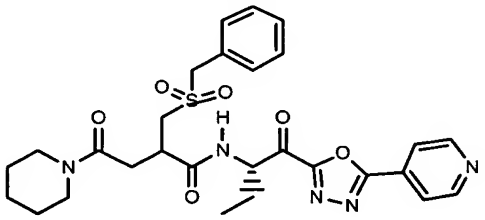
To a stirred mixture of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (106.5mg, 0.3mmol), 2-Amino-1-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-butan-1-ol TFA salt (105mg), prepared as in reference 18, and HOBt (55mg, 0.36mmol) in $MeCl_2$ (5ml), was added EDC (86.4mg, 0.45mmol) and N-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated, yield 176 mg of *N*-{1-[hydroxy-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide. MS: 568.4(M-1), 570(M+1)

This amide was treated with Dess-Martin periodinane (222.7mg, 0.45mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 84mg of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; H^1 NMR(DMSO-d): 8.95-8.85(3H, m), 8.1-8(2H, m), 7.44-7.3(5H, m), 5-4.9(1H, m), 4.5-4.3(2H, m), 3.4-3.(8H, m), 2.7-2.5(1H, m), 2.05-1.9(1H, m), 1.8-1.6(1H, m), 1.6-1.2(6H, m), 0.98(3H, t); MS: 566.6(M-1), 568.6(M+1).

EXAMPLE 28

4-Oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide

(Compound 84)



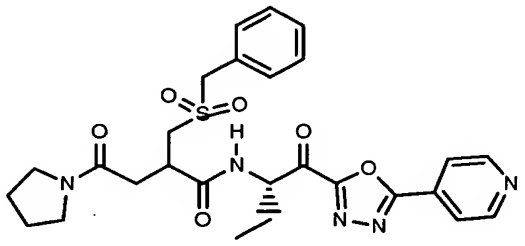
To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyric acid (105.9mg, 0.3mmol), 2-amino-1-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-butan-1-ol TFA salt (105mg) , prepared as in reference 18, and HOBt (55mg, 0.36mmol) in $MeCl_2$ (5ml), was added EDC (86.4mg, 0.45mmol) and *N*-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 176mg of *N*-{1-[Hydroxy-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-morpholin-4-yl-4-oxo-2-benzylsulfonyl-methyl-butyramide; MS: 570.2(M-1), 572(M+1).

This amide was treated with Dess-Martin periodinane (222.7mg, 0.45mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 78 mg of 4-oxo-2-benzylsulfonyl-methyl-4-piperidin-1-yl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; H^1 NMR(DMSO-d): 9.0-8.85(3H, m), 8.1-8(2H, m), 7.44-7.3(5H, m), 5-4.9(1H, m), 4.5-4.3(2H, m), 3.6-3.2(11H, m), 3.15-3.05(1H, m), 2.7-2.5(1H, m), 2.05-1.9(1H, m), 1.8-1.7(1H, m), 0.96(3H, t); MS: 568.6(M-1), 570.6(M+1).

EXAMPLE 29

4-Oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-pyrrolidin-1-yl-butyramide

(Compound 85)



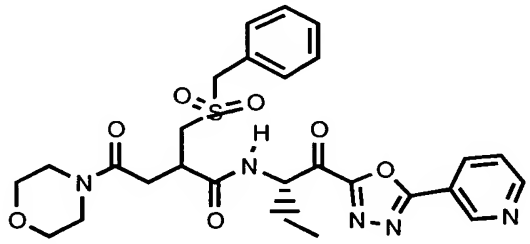
To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyric acid (102mg, 0.3mmol), 2-amino-1-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-butan-1-ol TFA salt (105mg) , prepared as in reference 18, and HOBt (55mg, 0.36mmol) in $MeCl_2$ (5ml), was added EDC (86.4mg, 0.45mmol) and *N*-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 210 mg of *N*-{1-[Hydroxy-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide. MS: 554.2(M-1), 555.8(M+1).

This amide was treated with Dess-Martin periodinane (222.7mg, 0.45mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 102 mg of 4-Oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-pyrrolidin-1-yl-butyramide; H^1 NMR (DMSO-d): 9.0-8.85(3H, m), 8.1-8(2H, m), 7.44-7.3(5H, m), 5.05-4.9(1H, m), 4.55-4.35(2H, m), 3.4-3.(8H, m), 2.6-2.4(1H, m), 2.05-1.9(1H, m), 1.9-1.6(5H, m), 0.96(3H, t); MS: 552.6(M-1), 554.6(M+1).

EXAMPLE 30

4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide

(Compound 86)



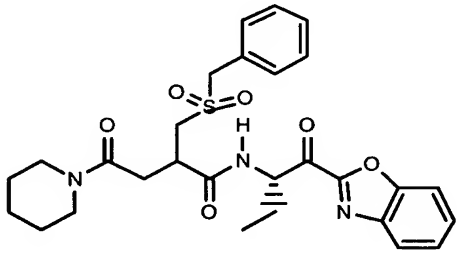
To a stirred mixture of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid (177.7mg, 0.5mmol), 2-amino-1-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-butan-1-ol TFA salt (180mg), prepared as in reference 19, and HOBt (92mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and *N*-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated, yield 210 mg of *N*-{1-[Hydroxy-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-methyl]-propyl}-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide. Without further purification, the crude product was used for next reaction; MS: 570.4(M-1), 572.4(M+1).

This amide was treated with Dess-Martin periodinane (277mg, 0.56mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 110 mg of 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; H^1 NMR(DMSO-d: 9.23(1H, s), 8.94, 8.88(1H, d,d, NH, diastereomeric), 8.87-8.8(1H, m), 8.46-8.4(1H, m), 7.7-7.6(1H, m), 7.4-7.25(5H, m), 5.05-4.9(1H, m), 4.55-4.3(2H, m), 3.6-3.15(11H, m), 3.14-3(1H, m), 2.7-2.5(1H, m), 2.05-1.9(1H, m), 1.8-1.65(1H, m), 0.98(3H, t); MS: 568.5(M-1), 570.3(M+1).

EXAMPLE 31

N-[1-(Benzooxazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide

(Compound 87)



To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyric acid (141mg, 0.4mmol), 2-amino-1-benzooxazol-2-yl-butan-1-ol TFA salt. (129mg), prepared as in reference 20, and HOBt (74mg, 0.48mmol) in $MeCl_2$ (5ml), was added EDC (115mg, 0.6mmol) and N-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 157mg of *N*-[1-(Benzooxazol-2-yl-hydroxy-methyl)-propyl]-4-oxo-2-enylmethylsulfonylmethyl-4-piperidin-1-yl-butyramide. Without further purification, the crude product was used for next reaction; MS: 540.4(M-1), 542.6(M+1).

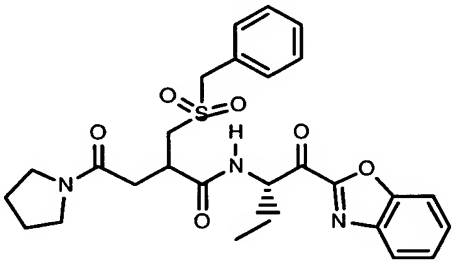
This amide was treated with Dess-Martin periodinane (215.3mg, 0.435mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 103.3 mg of *N*-[1-(Benzooxazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide; H^1 NMR(DMSO-d): 8.84, 8.76(1H, d,d, J=5.6Hz, J=6.4Hz, NH, diastereomeric), 8.02-7.96(1H, m), 7.92-7.86(1H, m), 7.68-7.62(1H, m), 7.58-7.52(1H, m), 7.44-7.32(5H, m), 5.24-5.12(1H, m), 4.52-4.38(2H, m), 3.5-3.22(7H, m), 3.12-3.02(1H, m), 2.64-2.52(1H, m), 2.04-1.94(1H, m),

1.8-1.68(1H, m), 1.6-1.48(2H, m), 1.48-1.32(4H, m), 0.98(3H, t, J=7.6Hz); MS: 540.4(M+1).

EXAMPLE 32

N-[1-(Benzooxazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide

(Compound 88)



To a stirred mixture of 4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyric acid (135.6mg, 0.4mmol), 2-amino-1-benzooxazol-2-yl-butan-1-ol TFA salt (129mg) , prepared as in reference 20, and HOBt (73.4mg, 0.48mmol) in $MeCl_2$ (5ml), was added EDC (115.2mg, 0.6mmol) and *N*-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 260 mg of *N*-[1-(Benzooxazol-2-yl-hydroxy-methyl)-propyl]-4-oxo-2-henylmethylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide. Without further purification, the crude product was used for next reaction; MS: 526.6(M-1), 528.6(M+1).

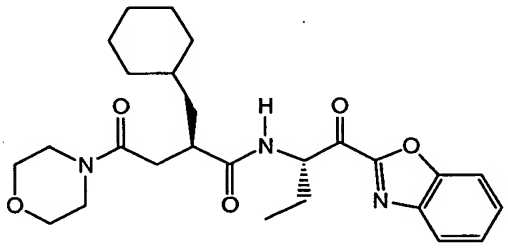
This amide was treated with Dess-Martin periodinane (215mg, 0.435mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 199mg of *N*-[1-(Benzooxazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide; H^1 NMR(DMSO-d): 8.87, 8.79(1H, d,d, NH, J=6Hz, J=6.4Hz, diastereomeric), 8.04-7.96(1H, m), 7.92-7.86(1H, m),

7.68-7.62(1H, m), 7.58-7.5(1H, m), 7.44-7.32(5H, m), 5.25-5.14(1H, m), 4.52-4.38(2H, m), 3.5-3.04(7H, m), 3.03-3.01(1H, m), 2.52-2.4(1H, m), 2.05-1.9(1H, m), 1.9-1.65(5H, m), 0.98(3H, m); MS: 526.3(M+1).

EXAMPLE 33

N-[1-(Benzooxazole-2-carbonyl)-propyl]-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyramide

(Compound 89)



To a stirred mixture of 2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid (84.9mg, 0.3mmol), 2-amino-1-benzooxazol-2-yl-butan-1-ol TFA salt(96.9mg), prepared as in reference 21, and HOBt (55.1mg, 0.36mmol) in $MeCl_2$ (5ml), was added EDC (86.4mg, 0.45mmol) and *N*-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 150 mg of *N*-[1-(benzooxazol-2-yl-hydroxy-methyl)-propyl]-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyramide; MS: 470.5(M-1), 472.4(M+1).

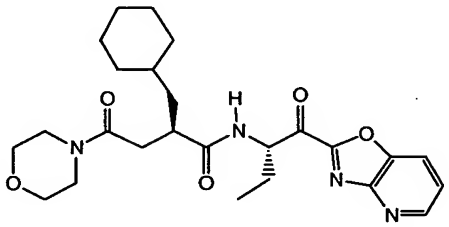
This amide was treated with Dess-Martin periodinane (237.6mg, 0.48mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 76 mg of *N*-[1-(benzooxazole-2-carbonyl)-propyl]-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyramide; H^1 NMR(DMSO-d): 8.49(1H, d, J=5.2Hz, NH), 7.96(1H, d, J=7.6Hz), 7.86(1H, d, J=8.4), 7.6(1H, m), 7.5(1H,

m), 5.14-5.04(1H, m), 3.6-3.25(8H, m), 2.9-2.75(1H, m), 2.5-2.4(1H, m), 2.25-2.15(1H, m), 2-1.8(1H, m), 1.8-1.7(2H, m), 1.7-1.6(1H, m), 1.6-1.4(5H, m), 1.35-1.2(1H, m), 1.2-1(4 H, m), 0.96(3H, t); MS: 468.6(M-1), 470.5(M+1), 492.3(M+Na).

EXAMPLE 34

2-Cyclohexylmethyl-4-morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide

(Compound 90)



To a stirred mixture of 2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid (84.9mg, 0.3mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-butanol TFA salt (97.5mg), prepared as in reference 21, and HOBt (55.1mg, 0.36mmol) in $MeCl_2$ (5ml), was added EDC (86.4mg, 0.45mmol) and *N*-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 153mg of 2-cyclohexylmethyl-*N*-[1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-4-morpholin-4-yl-4-oxo-butyramide; MS: 471.6(M-1), 473.3(M+1).

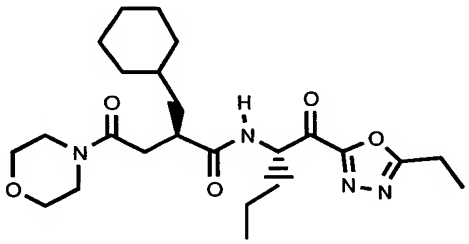
This amide was treated with Dess-Martin periodinane (237.6mg, 0.48mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 95 mg of 2-cyclohexylmethyl-4-morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide; H^1 NMR(DMSO-d): 8.72-8.68(1H, m), 8.6(1H, d, J=5.2Hz, NH), 8.4-8.34(1H, m), 7.68-7.59(1H, m), 5.2-

4.96(1H, m), 3.5-3.45(8H, m), 2.58(1H, m), 2.5-2.4(1H, m), 2.45-2.15(1H, m), 2.05-1.9(1H, m), 1.85-1.65(2H, m), 1.6-1.4(5H, m), 1.3-1.2(1H, m), 1.25-1(4H, m), 0.97(3H, t); MS: 469.6(M-1), 471.4(M+1), 493.2(M+Na).

EXAMPLE 35

2-Cyclohexylmethyl-N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide

(Compound 91)



To a stirred mixture of 2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid (84.9mg, 0.3mmol), 2-amino-1-(5-ethyl-1,3,4-oxadiazole-2-yl)-1-pentanol HCl salt (70.5mg), prepared as in reference 21, and HOBt (55.1mg, 0.36mmol) in $MeCl_2$ (5ml), was added EDC (86.4mg, 0.45mmol) and *N*-methylmorpholine (0.25ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 142 mg of 2-cyclohexylmethyl-*N*-{1-[(5-ethyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-butyl}-4-morpholin-4-yl-4-oxo-butyramide; MS: 463.5(M-1), 465.3(M+1).

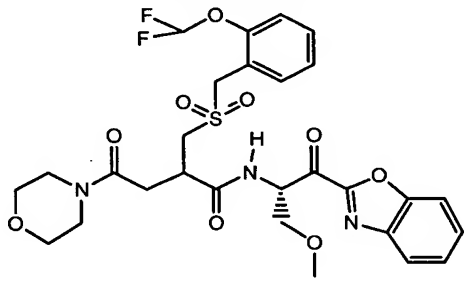
This amide was treated with Dess-Martin periodinane (239mg, 0.48mmol) at room temperature. After stirring for 1 hour, 5mls of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 65 mg of 2-cyclohexylmethyl-N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide; H^1 NMR

(DMSO-d): 8.6, 8.51(1H, dd, J=6.8Hz, J=5.6Hz, NH, diastereomeric), 4.98(-4.88(1H, m), 3.6-3.25(8H, m), 3-2.9(2H, q, J=7.6Hz), 2.9-2.75(1H, m), 2.5-2.4(1H, m), 2.3-2.1(1H, m), 1.9-1.7(2H, m), 1.7-1.4(7H, m), 1.4-1.2(2H, m), 1.28(3H, t), 1.2-1(6H, m), 0.88(3H, t); MS: 461.4(M-1), 463.4(M+1), 485.4(M+Na).

EXAMPLE 36

N-(2-Benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethyl)-2-(2-difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide

(Compound 92)



To a stirred mixture of 2-(2-difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyric acid (210.5mg, 0.5mmol), 2-amino-1-benzooxazol-2-yl-3-methoxy-propan-1-ol (112.5mg), and HOBt (91.8mg, 0.6mmol) in $MeCl_2$ (5ml), was added EDC (144mg, 0.75mmol) and N-methylmorpholine (0.35ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 301mg of *N*-(2-benzooxazol-2-yl-2-hydroxy-1-methoxymethyl-ethyl)-2-(2-difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; MS: 624.5(M-1), 626.3(M+1).

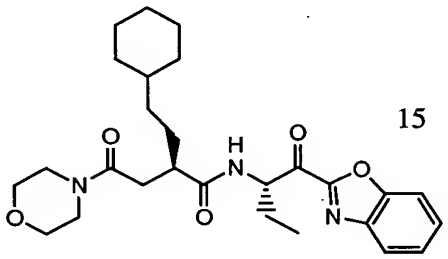
This amide(150mg, 0.24mmol) was treated with Dess-Martin periodinane (178mg, 0.36mmol) at room temperature. After stirring for 1 hour, 5ml of saturated $Na_2S_2O_3$-$NaHCO_3$ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography to yield 39 mg of *N*-(2-Benzooxazol-2-yl-

1-methoxymethyl-2-oxo-ethyl)-2-(2-difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; H^1 NMR(DMSO-d): 8.97, 8.8(1H, dd, J=5.6Hz, J=5.6Hz, NH, diastereomeric), 8.02-7.94(1H, m), 7.9-7.84(1H, m), 7.66-7.58(1H, m), 7.55-7.38(3H, m), 7.3-7.18(2H, m), 7.1(1H, t, J=73.6Hz), 5.54-5.42(1H, m), 4.6-4.4(4H, m), 3.92-3.84(1H, m), 3.82-3.72(1H, m), 3.68-3.1(11H, m), 2.7-2.56(1H, m), 1.7-1.55(1H, m), 1.3-1(1H, m); MS: 622.4(M-1), 624.3(M+1), 646.3(M+Na).

EXAMPLE 37

N-[1-(Benzooxazole-2-carbonyl)-propyl]-2-(2-cyclohexyl-ethyl)-4-morpholin-4-yl-4-oxo-butyramide

(Compound 93)

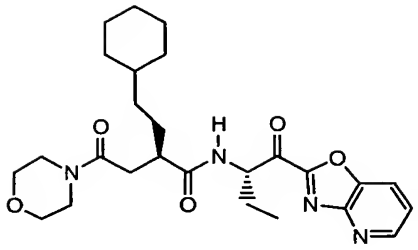


^{1}H NMR: (DMSO) 8.47 (d, J=6Hz, 1H), 7.96 (d, J=8.2Hz, 1H), 7.86 (d, J=8.2Hz, 1H), 7.59 (t, J=8.2Hz, 1H), 7.51 (t, J=8.2Hz, 1H), 5.09-5.03 (m, 1H), 3.56-3.27 (m, 8H), 2.72-2.64 (m, 1H), 2.54-2.46 (m, 1H), 2.21 (dd, J=15.8Hz, J=5.3Hz, 1H), 1.99-1.89 (m, 1H), 1.76-1.65 (m, 1H), 1.60-0.95 (m, 13H), 0.96 (t, J=7Hz, 3H), 0.72-0.60 (m, 2H). MS: $(M+H)^+$ 484.

EXAMPLE 38

2-(2-Cyclohexyl-ethyl)-4-morpholin-4-yl-*N*-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide

(Compound 94)

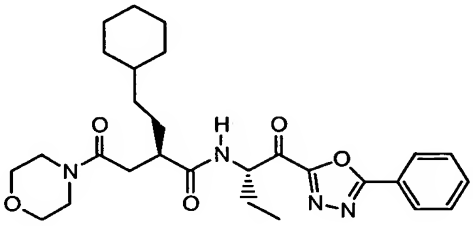


^{1}H NMR: (DMSO) 8.71-8.68 (m, 1H), 8.58 (d, J=4.7Hz, 1H), 8.36 (d, J=8.5Hz, 1H), 7.66-7.61 (m, 1H), 5.00-4.93 (m, 1H), 3.56-3.26 (m, 8H), 2.72-2.63 (m, 1H), 2.54-2.44 (m, 1H), 2.20 (dd, J=15.8Hz, J=5.3Hz, 1H), 2.02-1.92 (m, 1H), 1.78-1.67 (m, 1H), 1.60-0.95 (m, 13H), 0.97 (t, J=7Hz, 3H), 0.68-0.57 (m, 2H). MS: $(M+H)^+$ 485.

EXAMPLE 39

2-(2-Cyclohexyl-ethyl)-4-morpholin-4-yl-4-oxo-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide

(Compound 95)

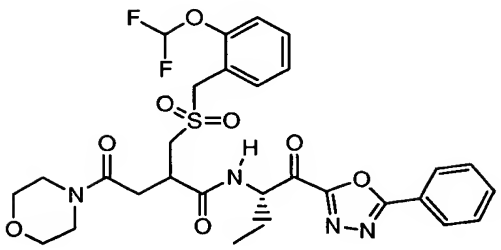


^{1}H NMR: (DMSO) 8.54 (d, J=4.7Hz, 1H), 8.10-8.04 (m, 2H), 7.70-7.58 (m, 3H), 4.91-4.85 (m, 1H), 3.55-3.22 (m, 8H), 2.70-2.62 (m, 1H), 2.56-2.45 (m, 1H), 2.22 (dd, J=15.5Hz, J=5Hz, 1H), 1.98-1.88 (m, 1H), 1.77-1.66 (m, 1H), 1.60-0.95 (m, 13H), 0.96 (t, J=7Hz, 3H), 0.75-0.60 (m, 2H). MS: $(M+H)^+$ 511.

EXAMPLE 40

2-(2-Difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-*N*-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide

(Compound 96)

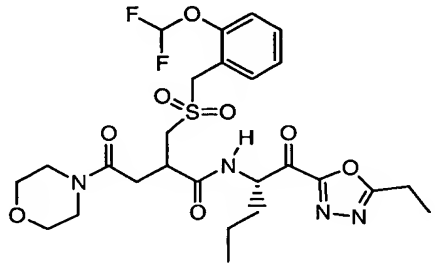


1:1 Mixture of diastereomers. ^{1}H NMR: (DMSO), 8.89 (d, J=5.6Hz), 8.82 (d, J=6Hz) 1H], 8.08-8.03 (m, 2H), 7.70-7.18 (m, 7H),, 7.11 (t, JH,F=74Hz), 7.08 (t, JH,F=74Hz) 1H], 5.01-4.90 (m, 1H), 4.56-4.43 (m, 2H), 3.56-3.13 (m, 10H), 2.68-2.40 (m, 3H), 2.00-1.90 (m, 1H), 1.78-1.68 (m, 1H), 0.96 (t, J=7Hz, 3H). MS: $(M+H)^+$ 635.

EXAMPLE 41

2-(2-Difluoromethoxy-benzylsulfonylmethyl)-*N*-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide

(Compound 97)

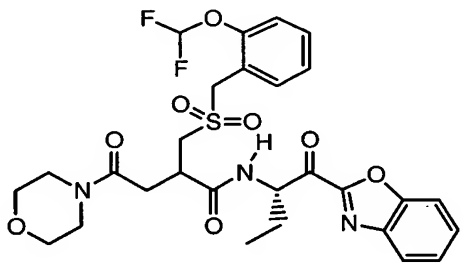


1:1 Mixture of diastereomers. ^{1}H NMR: (DMSO), 8.82 (d, J=5.5Hz), 8.77 (d, J=5Hz) 1H], 7.51-7.42 (m, 2H), 7.30-7.19 (m, 2H),, 7.11 (t, JH,F=74Hz), 7.10 (t, JH,F=74Hz) 1H], 5.02-4.92 (m, 1H), 4.56-4.43 (m, 2H), 3.58-3.26 (m, 10H), 3.20-3.12 (m, 1H), 2.98-2.89 (m, 2H), 2.68-2.44 (m, 2H), 1.86-1.76 (m, 1H), 1.69-1.58 (m, 1H), 1.46-1.20 (m, 5H), 0.88 (t, J=7Hz, 3H). MS: $(M+H)^+$ 601.

EXAMPLE 42

N-[1-(Benzooxazole-2-carbonyl)-propyl]-2-(2-difluoromethoxy-benzyl-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide

(Compound 98)

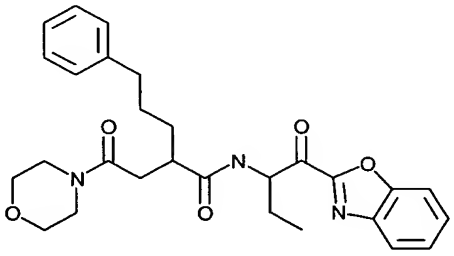


1:1 Mixture of diastereomers. ^{1}H NMR: (DMSO), 8.85 (d, J=5.3Hz), 8.76 (d, J=5.3Hz) 1H], 7.97 (t, J=6.5Hz, 1H), 7.89-7.84 (m, 1H), 7.64-7.18 (m, 6H),, 7.12 (t, JH,F=74Hz), 7.10 (t, JH,F=74Hz) 1H], 5.22-5.11 (m, 1H), 4.56-4.42 (m, 2H), 3.58-3.12 (m, 11H), 2.67-2.42 (m, 2H), 2.02-1.92 (m, 1H), 1.78-1.66 (m, 1H), 0.96 (t, J=7Hz, 3H). MS: $(M+H)^+$ 608.

EXAMPLE 43

2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzooxazole-2-carbonyl)-propyl]-amide

(Compound 99)



2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid (83.7 mg, 0.274 mmol),

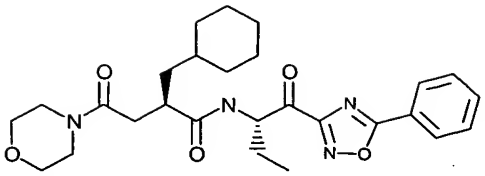
prepared as in reference 25, and HOBT (62.9 mg, 0.466 mmol) were added to a suspension of PS-bound N-Cyclohexylcarbodiimide (HL 200-400mesh cross linked with 2% DVB) from Novabiochem (322.3 mg, 0.548 mmol, 1.7 mmol/g loading) in methylene chloride (8 ml) and stirred at room temperature for 15 minutes. 2-Amino-1-benzooxazol-2-yl-butan-1-ol (56.5 mg. 0.274 mmol), prepared as in reference 20, was added and the reaction mixture stirred overnight at room temperature. Silicycle trisamine-3 (380.5 mg, 1.37 mmol, 3.6 mmol/g loading) was added and stirred for another 2 hours. The mixture was filtered and the filtrate evaporated under reduced pressure to give 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzooxazol-2-yl-hydroxy-methyl)-propyl]-amide as a yellow solid (128 mg).

To a solution of 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzooxazol-2-yl-hydroxy-methyl)-propyl]-amide (128 mg, 0.259 mmol) in methylene chloride (5 ml), Dess-Martin Periodinane (0.519 mmol, 220 mg) was added and stirred at room temperature for 90 minutes. The reaction mixture was washed with a solution of $Na_2S_2O_3$ in saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography, eluting with a mixture of ethyl acetate and heptane, to give 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzooxazole-2-carbonyl)-propyl]-amide as a mixture of diastereoisomers (77 mg); ^1H NMR ($CDCl_3$) 7.90 (d, J=8Hz, 1H), 7.65 (d, J=8.2Hz, 1H), 7.55 (t, J=7.3Hz, 1H), 7.46 (t, J=7.2Hz, 1H), 7.4-7.1 (m, 5H),, 7.0 (d, J=7.4Hz), 6.76 (d, J=7.1Hz), 1H], 5.60 (m, 1H), 3.8-3.4 (m, 8H), 3.1-2.5 (m, 4H), 2.4-2.1 (m, 2H), 2.0-1.6 (m, 4H), 1.5 (m, 1H), 1.1 (m, 3H). MS : 492 (MH^+).

EXAMPLE 44

(R)-2-Cyclohexylmethyl-4-morpholin-4-yl-4-oxo-*N*-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-butyramide

(Compound 100)

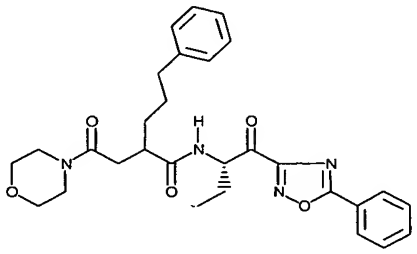


Similarly prepared according to the general procedure given for Example 43 but using (R)-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid, prepared as described in reference 21, and (S)-2-amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol, prepared as in reference 26; MS: 519 (M+Na), LC-MS retention time 4.5 min; ^{1}H NMR ($CDCl_3$) 8.19 (d, J =7Hz, 2H), 7.65-7.51 (m. 3H), 6.64 (d, J=7Hz, 1H), 5.44-5.38 (m, 1H), 3.69-3.38 (m, 8H), 3.05-2.98 (m, 1H), 2.76 (dd, J=16Hz &10Hz, 1H), 2.26 (dd, J=16Hz & 3Hz, 1H), 2.10 (m, 1H), 1.80 (m, 1H), 1.75-1.59 (m, 6H), 1.28-1.13 (m, 5H), 1.03-0.98 (t, J = 7Hz, 3H), 0.92-0.81 (m, 2H).

EXAMPLE 45

2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, (S)-1-(5-phenyl-[1,2,4]oxadiazole-3-carbonyl)-propyl]-amide

(Compound 101)



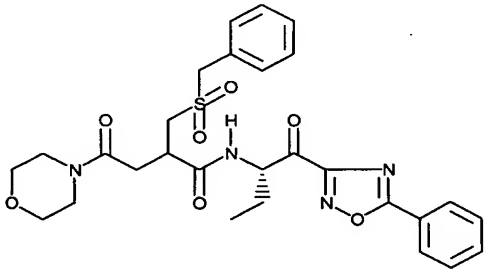
Similarly prepared according to the procedure for Example 43 but using 2-(2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid and (S)-2-amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol; MS : 541 (M+Na), LCMS retention time 4.44 and 4.53 min; ^{1}H NMR ($CDCl_3$) 8.18 (d, J= 7Hz, 2H), 7.69-7.51 (m, 3H), 7.27-7.10 (m, 5H), 6.99-6.7 (d, J=7Hz, 1H), 5.38 (m, 1H), 3.70-3.36 (m, 8H), 2.99-2.56 (m, 4H), 2.27 (m, 1H), 2.11

(m, 1H), 1.87-1.60 (m, 4H), 1.44 (m, 1H), 1.02-0.97(dt, J=7Hz, 3H).

EXAMPLE 46

4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-*N*-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-butyramide

(Compound 102)

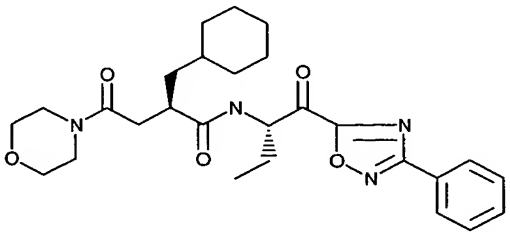


Similarly prepared according to the procedure for Example 43 but using 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid and (S)-2-amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol; MS: 569 (MH^+), LCMS retention time 4.1 min; ^1H NMR ($CDCl_3$) 8.18 (d, J= 7.9Hz, 2H), 7.74-7.31 (m, 9H), 5.27 (m, 1H), 4.25 (m, 2H), 3.71-3.41 (m, 8H), 2.95 (m, 1H), 2.78-2.70 (m, 2H), 2.10 (m, 1H), 1.85 (m, 1H), 1.0 (m, 3H).

EXAMPLE 47

(R)-2-Cyclohexylmethyl-4-morpholin-4-yl-4-oxo-*N*-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-butyramide

(Compound 103)

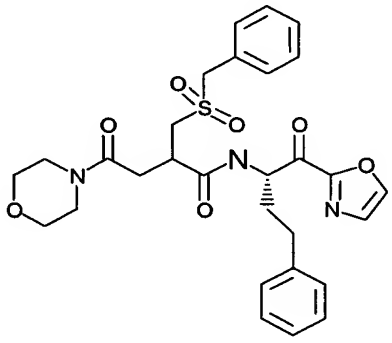


Similarly prepared according to the general procedure given for Example 43 above but using (R)-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid and (S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol; MS: 497 (MH^+).

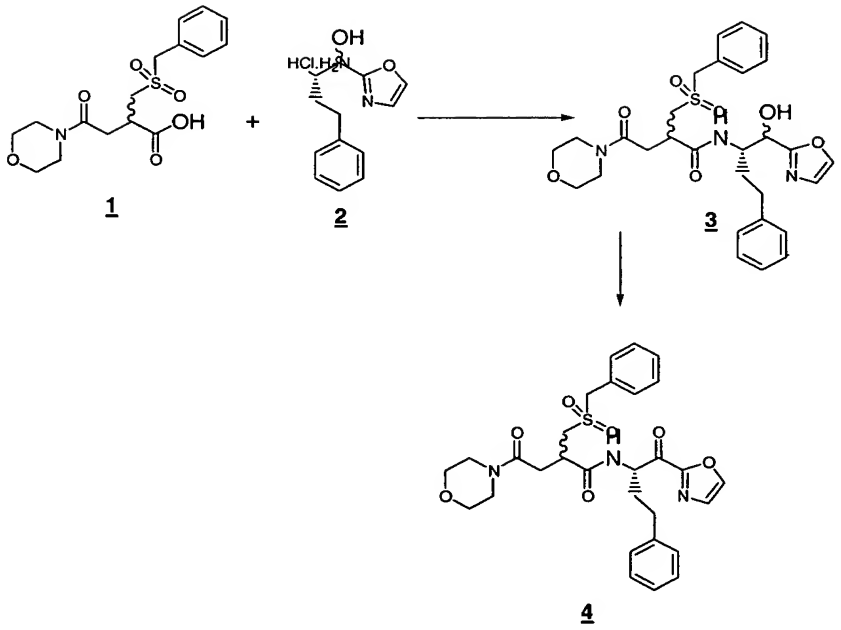
EXAMPLE 48

4-Morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-2-benzylsulfonylmethyl-butyramide

(Compound 104)



Compound 104 was synthesized according to the following reaction protocol:

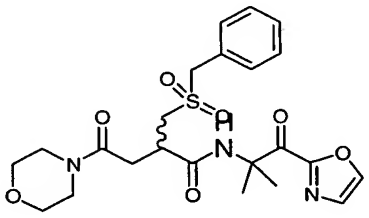


Compound 1 (0.1066g, 0.3mmol) and compound 2 (0.0806g, 0.3mmol) were mixed with EDC (0.0633g,0.33mmol), HOBT (0.0446g, 0.33mmol) and DIEA (0.2ml, 1.2mmol) in 3 ml of DMF which was stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed with cold 1N HCl, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified using a 10g silica gel column eluting with 10% ethyl acetate/n-heptane to 80% ethyl acetate/n-heptane to give 79.4 mg (46%) of product 3. Compound 3 (73mg, 0.13mmol) was then dissolved in 1 ml of methylene chloride and Dess-Martin periodinane (15% in methylene chloride, 0.7358 g) was added and the reaction was allowed to at room temperature for 3 hours and excess Dess-Martin reagent was consumed by adding sodium thiosulfate in saturated sodium bicarbonate. The product was extracted with ethyl acetate and the organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified using a 10g silica gel column eluting with 100% n-heptane to 30% n-heptane/ethyl acetate to yield 32.2 mg (44%) of the final compound 4; LCMS retention time 3:57 minutes, M+1(568.2).

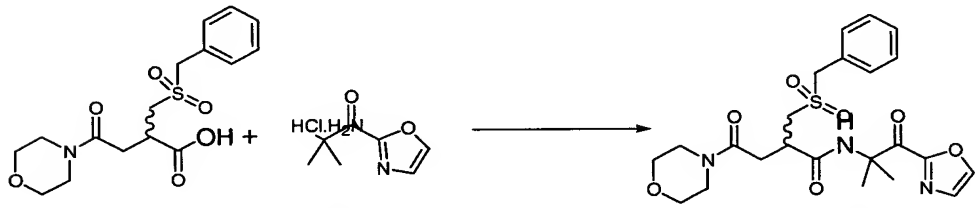
EXAMPLE 49

N-(1,1-Dimethyl-2-oxazol-2-yl-2-oxo-ethyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide

(Compound 105)



Compound 105 was synthesized according to the following reaction protocol:



1 **2** **3**

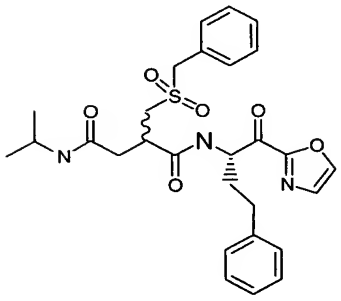
Compound **1** (0.1066g, 0.3mmol) and compound **2** (0.0572g, 0.3mmol) were mixed with EDC (0.0633g,0.33mmol), HOBT (0.0446g, 0.33mmol) and DIEA (0.2ml, 1.2mmol) in 3 ml of DMF which was stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed with cold 1N HCl, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified using a 10g silica gel column eluting with 10% ethyl acetate/n-heptane to 80% ethyl acetate/n-heptane to give 15 mg (10%) of final product **3**; LCMS retention time 3:10 minutes, M+1(492.2).

EXAMPLE 50

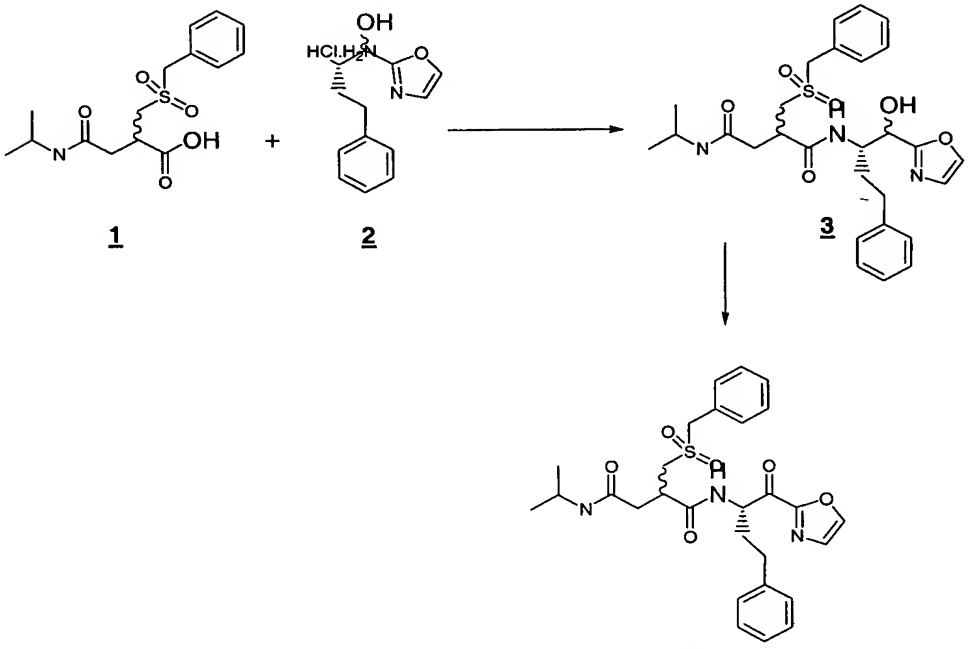
N-4-Isopropyl-*N*-1-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-2-benzylsulfonylmethyl-

succinamide

(Compound 106)



Compound 106 was synthesized according to the following reaction protocol:



1 2 3 4

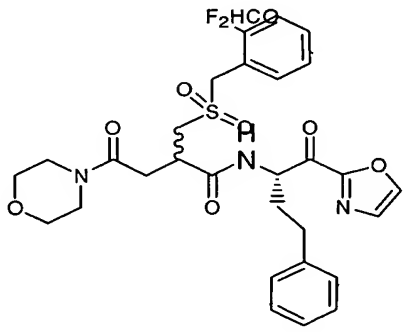
To a stirring suspension of N-Cyclohexylcarbodiimide, N'-methyl polystyrene resin (1.7 mmole/gram, 0.3529g, 0.6 mmol) in 10ml of methylene chloride was added the acid 1 (98.2 mg, 0.3mmol) and HOBT (69mg, 0.51mmol) which was allowed to stir for 15

minutes at room temperature. Compound **2** (80.6 mg, 0.3mmol) and DIEA (0.1ml, 0.5mmol) were added and the reaction was allowed to stir for 5 hours at room temperature. Then silicycle triamine™ (0.42g, 1.5mmol) was added and the reaction was stirred overnight at room temperature. The reaction was filtered and the solvent was removed under reduced pressure. The crude product **3** was used without further purification. Crude compound **3** was dissolved in methylene chloride and Dess-Martin reagent (15% in methylene chloride, 1.13g, 0.6mmol) was added and the reaction was allowed to stir at room temperature for 3 hours. The excess Dess-Martin reagent was consumed by adding sodium thiosulfate in saturated sodium bicarbonate. The product was extracted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified using HPLC to yield 15 mg of final compound **4**; LCMS retention time 3:07 minutes, M+1(540.2).

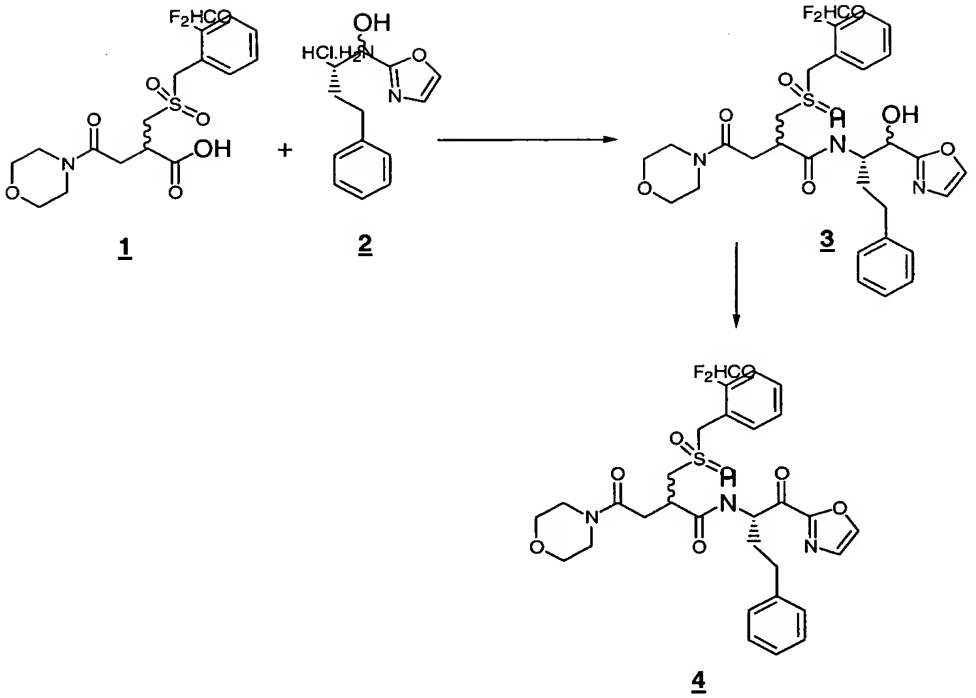
EXAMPLE 51

2-(2-Difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide

(Compound 107)



Compound 107 was synthesized according to the following reaction protocol:



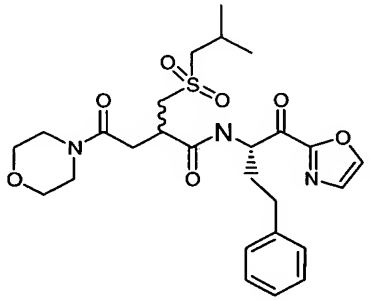
1 2 3 4

To a stirring suspension of *N*-Cyclohexylcarbodiimide, *N'*-methyl polystyrene resin (1.7 mmole/gram, 0.2353g, 0.4 mmol) in 10ml of methylene chloride was added the acid **1** (84.3 mg, 0.2mmol) and HOBT (45.9mg, 0.34mmol) which was allowed to stir for 15 minutes at room temperature. Compound **2** (53.75 mg, 0.2mmol) and DIEA (0.068ml, 0.4 mmol) were added and the reaction was allowed to stir for 5 hours at room temperature. Then silicycle triamine™ (0.28g, 1.0mmol) was added and the reaction was stirred overnight at room temperature. The reaction was filtered and the solvent was removed under reduced pressure. The crude product **3** was used without further purification. Crude compound **3** was dissolved in methylene chloride and Dess-Martin reagent (15% in methylene chloride, 1.13g, 0.6mmol) was added and the reaction was allowed to stir at room temperature for 3 hours. The excess Dess-Martin reagent was consumed by adding sodium thiosulfate in saturated sodium bicarbonate. The product was extracted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified using HPLC to yield 6 mg of final compound **4**; LCMS retention time 3:09 minutes, M+1(634.4).

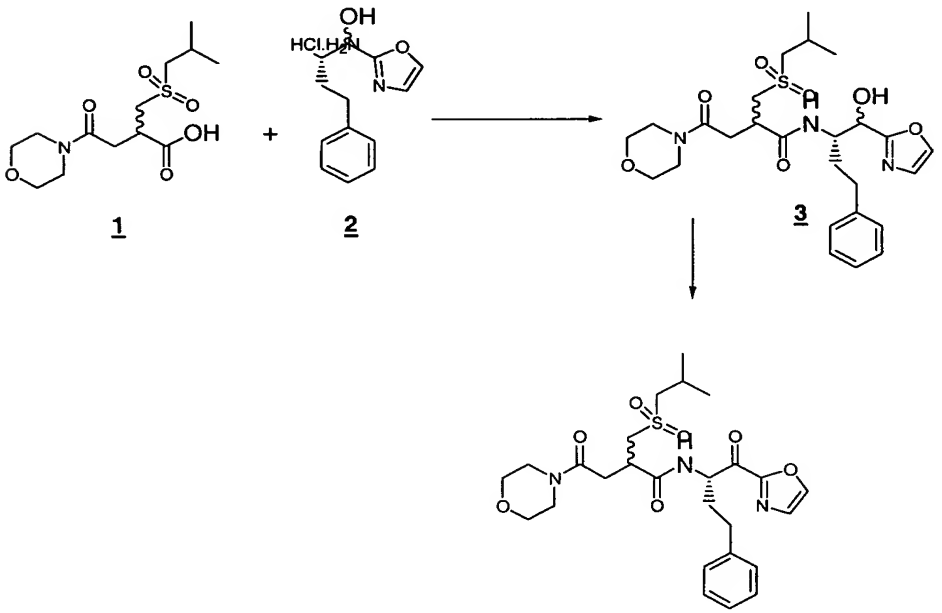
EXAMPLE 52

2-(2-Methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide

(Compound 108)



Compound 108 was synthesized according to the following reaction protocol:



1 2 3 4

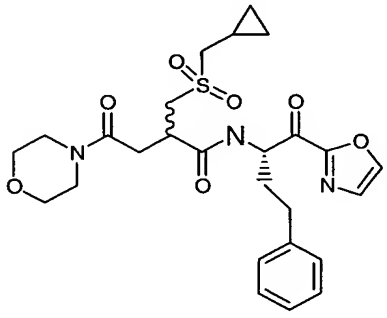
To a stirring suspension of *N*-Cyclohexylcarbodiimide, *N'*-methyl polystyrene resin (1.7 mmole/gram, 0.2353g, 0.4 mmol) in 10ml of methylene chloride was added the acid 1

(64.3 mg, 0.2mmol) and HOBT (45.9mg, 0.34mmol) which was allowed to stir for 15 minutes at room temperature. Compound **2** (53.75 mg, 0.2mmol) and DIEA (0.068ml, 0.4 mmol) were added and the reaction was allowed to stir for 5 hours at room temperature. Then silicycle triamine™ (0.28g, 1.0mmol) was added and the reaction was stirred overnight at room temperature. The reaction was filtered and the solvent was removed under reduced pressure. The crude product **3** was used without further purification. Crude compound **3** was dissolved in methylene chloride and Dess-Martin reagent (15% in methylene chloride, 1.13g, 0.6mmol) was added and the reaction was allowed to stir at room temperature for 3 hours. The excess Dess-Martin reagent was consumed by adding sodium thiosulfate in saturated sodium bicarbonate. The product was extracted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified using HPLC to yield 25.7 mg of final compound **4**; LCMS retention time 2:89 minutes, M+1(534.4).

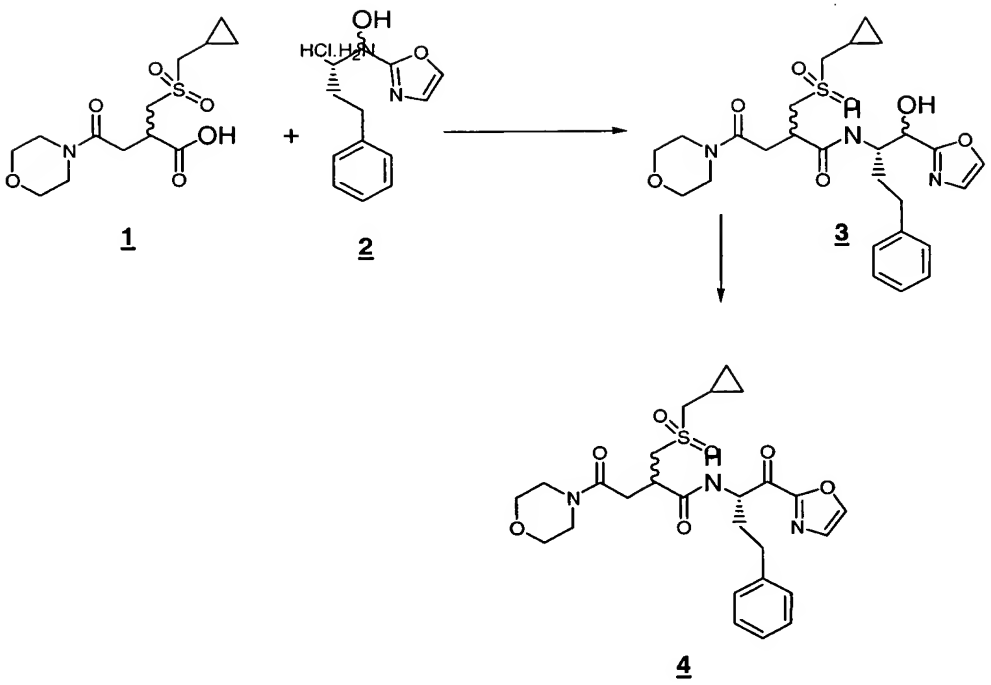
EXAMPLE 53

2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide

(Compound 109)



Compound 109 was synthesized according to the following reaction protocol:



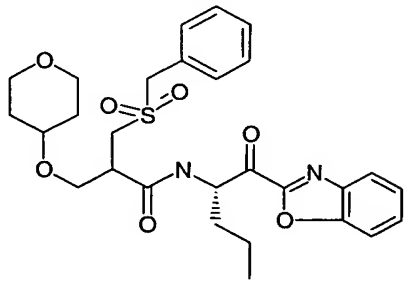
1 2 3 4

To a stirring suspension of *N*-Cyclohexylcarbodiimide, *N'*-methyl polystyrene resin (1.7 mmole/gram, 0.2353g, 0.4 mmol) in 10ml of methylene chloride was added the acid 1 (63.9 mg, 0.2mmol) and HOBT (45.9mg, 0.34mmol) which was allowed to stir for 15 minutes at room temperature. Compound 2 (53.75 mg, 0.2mmol) and DIEA (0.068ml, 0.4 mmol) were added and the reaction was allowed to stir for 5 hours at room temperature. Then silicycle triamine™ (0.28g, 1.0mmol) was added and the reaction was stirred overnight at room temperature. The reaction was filtered and the solvent was removed under reduced pressure. The crude product 3 was used without further purification. Crude compound 3 was dissolved in methylene chloride and Dess-Martin reagent (15% in methylene chloride, 1.13g, 0.6mmol) was added and the reaction was allowed to stir at room temperature for 3 hours. The excess Dess-Martin reagent was consumed by adding sodium thiosulfate in saturated sodium bicarbonate. The product was extracted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified using HPLC to yield 11.6 mg of final compound 4; LCMS retention time 2:77 minutes, M+1(532.4).

EXAMPLE 54

N-[1-(Benzooxazole-2-carbonyl)-butyl]-2-benzylsulfonyl-3-(tetrahydro-pyran-4-yloxymethyl)-propionamide

(Compound 110)



Diisopropylethylamine (0.184 ml, 1.05 mmol) was added to a mixture of 3-benzylsulfonyl-2-(tetrahydro-pyran-4-yloxymethyl)-propionic acid (362 mg, 1.05 mmol), prepared as in reference 27, and 2-amino-1-benzooxazol-2-yl-pentan-1-ol (238 mg, 1.05 mmol) and HATU (402 mg, 1.05 mmol) in DMF (10 ml) and stirred at room temperature overnight. Solvent was evaporated under reduced pressure, crude extract was taken up in ethyl acetate (30 ml) and washed with 1N HCl, saturated $NaHCO_3$ and brine. After drying over $MgSO_4$ the solvent was removed by rotary evaporation and the residue chromatographed on silica eluting with ethyl acetate/heptane mixture to give *N*-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-benzylsulfonylmethyl-3-(tetrahydro-pyran-4-yloxy)-propionamide (Yield: 258 mg); MS: 545 (M+1); LCMS retention time 3.71 and 3.76 minutes.

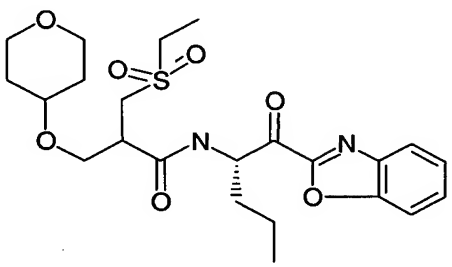
A solution of *N*-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-benzylsulfonylmethyl-3-(tetrahydro-pyran-4-yloxy)-propionamide (243 mg, 0.45 mmol) methylene chloride (8 ml) was treated with Dess-Martin periodinane (190 mg, 0.45 mmol) at room temperature for 2 hours. Washed with 0.26M solution of $Na_2S_2O_3$, $NaHCO_3$ and brine. After drying over $MgSO_4$ the solvent was removed by rotary evaporation and the residue chromatographed on silica eluting with ethyl acetate/heptane mixture to give *N*-[1-(benzooxazole-2-carbonyl)-butyl]-2-benzylsulfonyl-3-(tetrahydro-pyran-4-yloxymethyl)-propionamide as off white solid (Yield: 60 mg); MS: 543 (M+1); LCMS retention time 4.1

minutes.

EXAMPLE 55

N-[1-(Benzooxazole-2-carbonyl)-butyl]-3-ethanesulfonyl-2-(tetrahydro-pyran-4-yloxymethyl)-propionamide

(Compound 111)

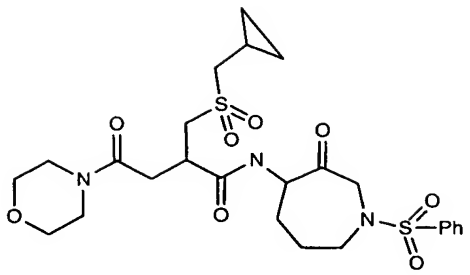


By following the method for Example 54 but substituting the required carboxylic acid with 3-ethylsulfonyl-2-(tetrahydro-pyran-4-yloxymethyl)-propionic acid, as prepared in reference 27b, *N*-[1-(benzooxazole-2-carbonyl)-butyl]-3-ethanesulfonyl-2-(tetrahydro-pyran-4-yloxymethyl)-propionamide was prepared. MS: 481 (M+1); LCMS retention time 3.7 minutes.

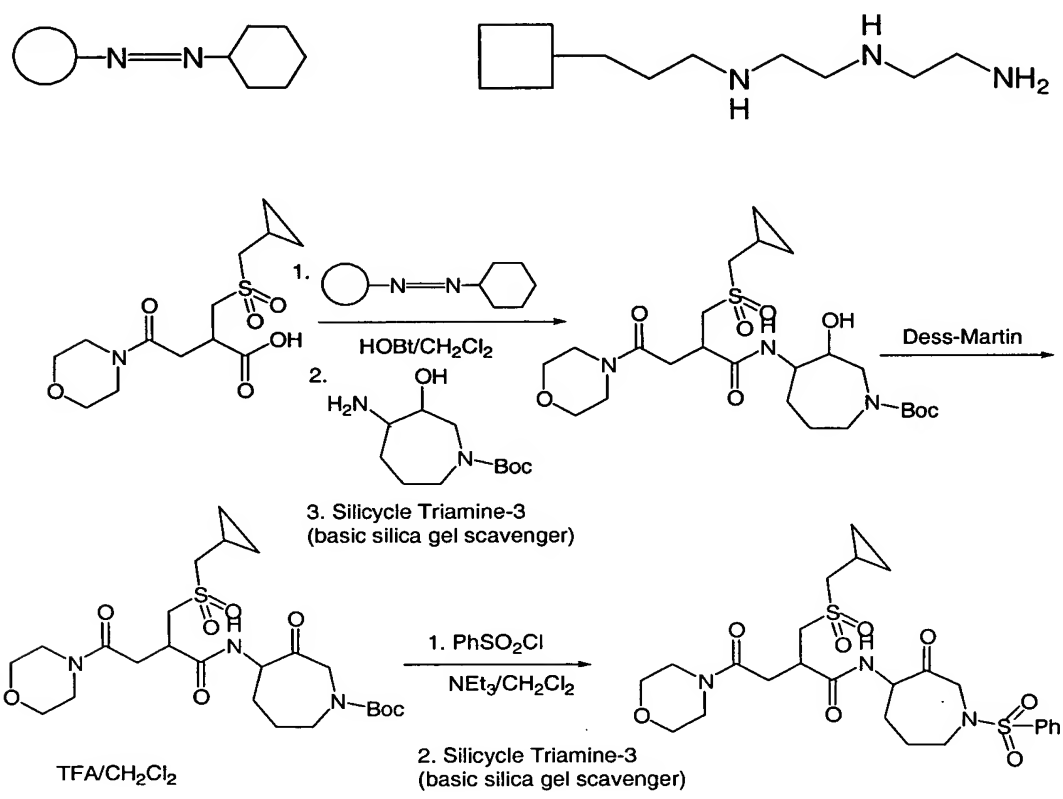
EXAMPLE 56

N-(1-Benzenesulfonyl-3-oxo-azepan-4-yl)-2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyramide

(Compound 112)



Compound 112 was prepared by the following protocol. The circle symbolizes the polystyrene backbone while the square symbolizes the silicium dioxide backbone:



1.16 mol-equivalents of the acid were dissolved in dichloromethyl. *N*-Cyclohexylcarbodiimide, *N*'-methylpolystyrene (2 mol-equivalents) and hydroxybenzotriazole (1.72 mol-equivalents) were added and the resulting reaction mixture stirred for 10 minutes. 4-Amino-3-hydroxy-azepane-1-carboxylic acid tert-butyl ester (1

mol-equivalent) was added and stirring continued for 21 hours. Silicycle-Triamine-3™ was added and the resulting mixture stirred for six hours. The mixture was filtered under suction and the filtrate concentrated under vacuum.

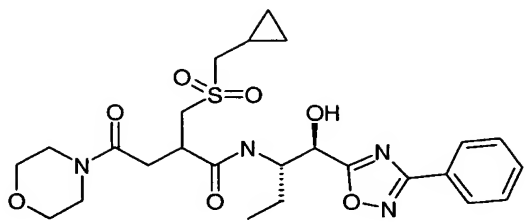
The alcohol was dissolved in dichloromethyl and 2 mol-equivalents of Dess-Martin periodinane were added to the solution. The reaction mixture was stirred for one hour. Equal volumes of saturated sodium thiosulfate solution and sat sodium bicarbonate solution were added and the phases separated. The aqueous phase was extracted three times with dichloromethyl. The combined organic phases were washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. The solution was dried with magnesium sulfate and the solvents evaporated.

The azepanone-1-carboxylic acid tert-butyl ester was dissolved in a dichloromethyl solution (20vol-%) of trifluoroacetic acid. After stirring for one hour dichloromethyl was removed under reduced pressure and trifluoroacetic acid under high vacuum. The solid residue was re-dissolved in dichloromethyl and five mol-equivalent of triethylamine were added. 1.2 mol-equivalent of benzenesulfonyl chloride were added and the reaction mixture stirred for four hours. 12 mol-equivalents of Silicycle Triamine™ were added and stirring continued for two hours. The mixture was filtered under suction and the dichloromethyl evaporated under reduced pressure. The crude product was purified via preparative HPLC yielding *N*-(1-benzenesulfonyl-3-oxo-azepan-4-yl)-2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyramide as an off-white solid; LC/MS retention time 2.61 minutes, m/z=570 (M+H).

The following examples were prepared according to methods described in Example 56:

2-Cyclopropylmethylsulfonylmethyl-N-{(S)-1-[(R)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-4-morpholin-4-yl-4-oxo-butyramide

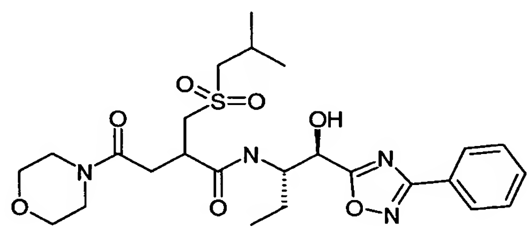
(Compound 122)



Tan solid; LC/MS retention time 3.456 minutes (TIC), m/z=557 (M+Na).

<u>*N*-{(S)-1-[(R)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide</u>

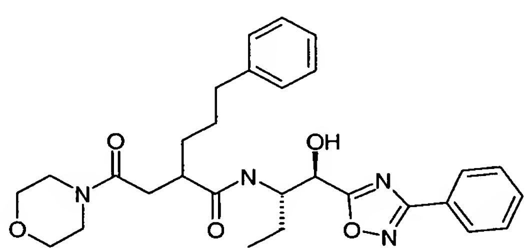
(Compound 123)



Tan solid; LC/MS retention time 3.594 minutes (TIC), m/z=559 (M+Na).

<u>2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid {(S)-1-[(R)-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-amide</u>

(Compound 124)

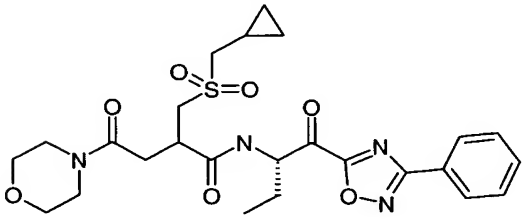


Tan solid; LC/MS retention time 3.379 minutes (TIC), m/z=521 (M+H).

<u>2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-N-[(S)-1-(3-phenyl-1,2,4-</u>

oxadiazole-5-carbonyl)-propyl]-butyramide

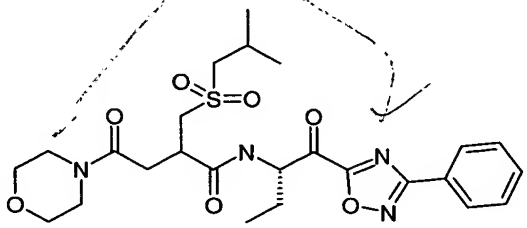
(Compound 125)



Tan solid; LC/MS retention time 2.976 minutes (TIC), m/z=533 (M+H).

2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-N-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-butyramide

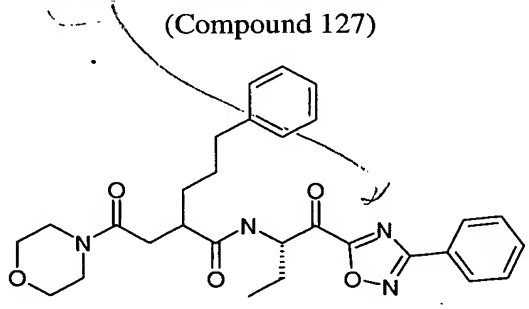
(Compound 126)



Tan solid; LC/MS retention time 3.433 minutes (TIC), m/z=535 (M+H).

2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, (S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl}-amide

(Compound 127)

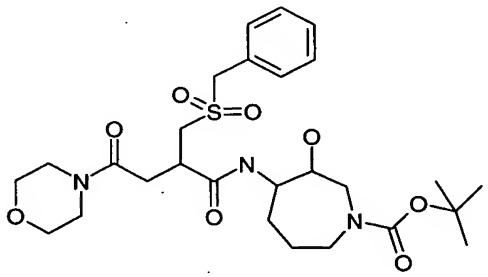


Tan solid; LC/MS retention time 3.762 minutes (TIC), m/z=519 (M+H).

EXAMPLE 57

3-Hydroxy-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-azepane-1-carboxylic acid tert-butyl ester

(Compound 113)

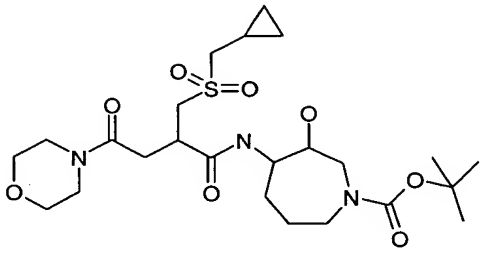


Tan solid prepared according to example 56; LC/MS retention time 2.985 minutes (TIC), m/z=568 (M+H) and 590 (M+Na).

EXAMPLE 58

4-(2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyrylamino)-3-hydroxy-azepane-1-carboxylic acid tert-butyl ester

(Compound 114)

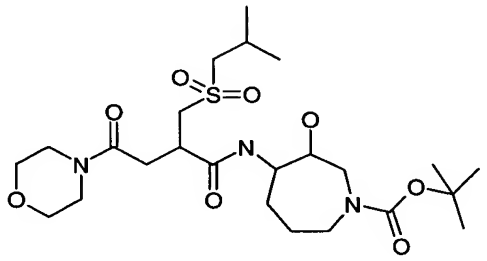


Tan solid prepared according example 56; LC/MS retention time 2.786 minutes (TIC), m/z=532 (M+H) and 554 (M+Na).

EXAMPLE 59

3-Hydroxy-4-[2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyrylamino]-azepane-1-carboxylic acid tert-butyl ester

(Compound 115)

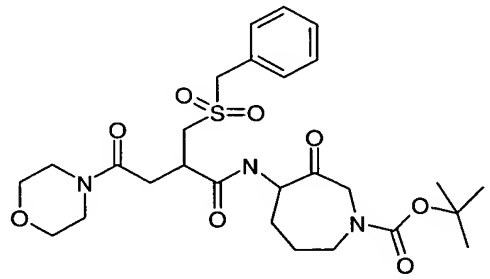


Tan solid prepared according example 56; LC/MS retention time 2.903 minutes (TIC), m/z=534 (M+H).

EXAMPLE 60

4-(4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-3-oxo-azepane-1-carboxylic acid tert-butyl ester

(Compound 116)

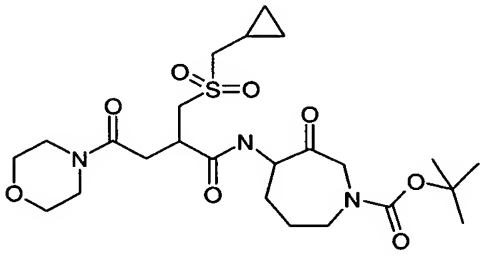


Tan solid prepared according example 56; LC/MS retention time 3.163 minutes (TIC), m/z=566 (M+H).

EXAMPLE 61

4-(2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyrylamino)-3-oxo-azepane-1-carboxylic acid tert-butyl ester

(Compound 117)

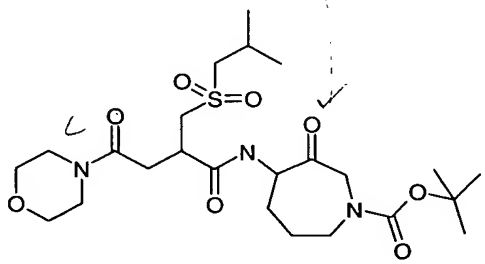


Tan solid prepared according to example 56; LC/MS retention time 2.965 minutes (TIC), m/z=530 (M+H).

EXAMPLE 62

4-[2-(2-Methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyrylamino]-3-oxo-azepane-1-carboxylic acid tert-butyl ester

(Compound 118)

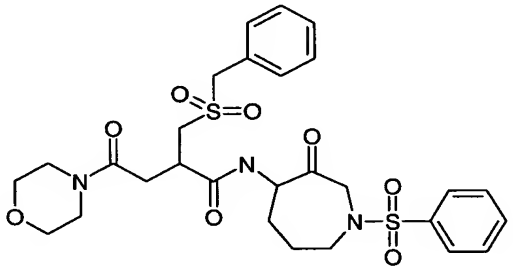


Tan solid prepared according to example 56; LC/MS retention time 3.083 minutes (TIC), m/z=532 (M+H).

EXAMPLE 63

N-(1-Benzenesulfonyl-3-oxo-azepan-4-yl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide

(Compound 119)

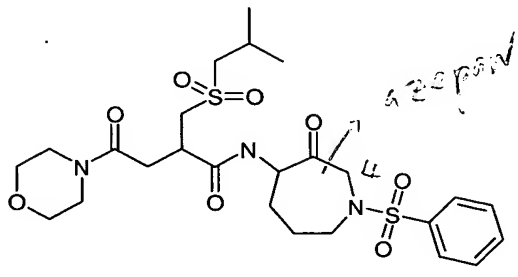


Off-white solid prepared according example 56; LC/MS retention time 2.83 minutes (TIC), m/z=606 (M+H).

EXAMPLE 64

N-(1-Benzenesulfonyl-3-oxo-azepan-4-yl)-2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide

(Compound 120)

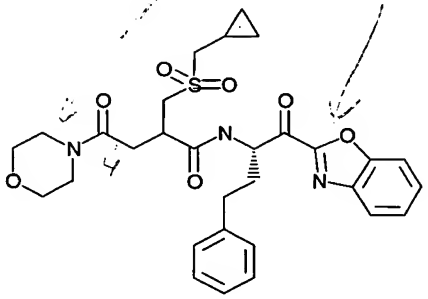


Off-white solid prepared according example 56; LC/MS retention time 2.72 minutes (TIC), m/z=572 (M+H).

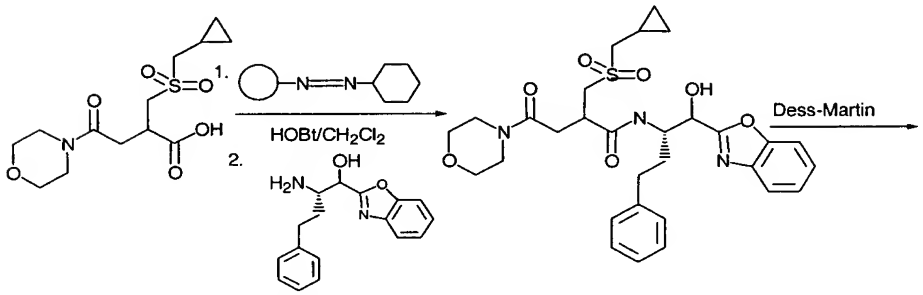
EXAMPLE 65

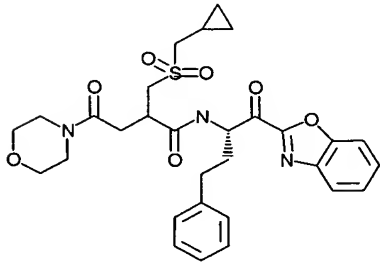
N-[(1S)-1-(Benzooxazol-2-yl-hydroxy-methyl)-3-phenyl-propyl]-2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyramide

(Compound 121)



Compound 121 was prepared according to the following reaction scheme:



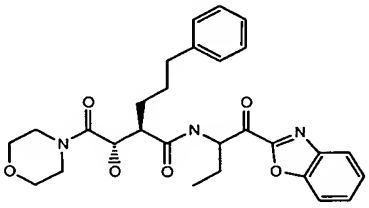


0.25mmol (1.16 mol-equivalent) of 2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyric acid was dissolved in 10ml dichloromethyl. 252mg, 0.43mmol *N*-cyclohexylcarbodiimide, *N'*-methylpolystyrene (2 mol-equivalents) and 50mg, 0.37mmol hydroxybenzotriazole (1.72 mol-equivalents) were added and the resulting reaction mixture stirred for 10 minutes. 61mg, 0.215mmol 2-amino-1-benzooxazol-2-yl-4-phenyl-butan-1-ol (1 mol-equivalents) was added and stirring continued for 21 hours. 510mg, 2.15mmol Silicycle-Triamine-3™ was added and the resulting mixture stirred for 6 hours. The mixture was filtered under suction and the filtrate concentrated under vacuum yielding 83mg, 0.142mmol (66%) of *N*-[(1S)-1-(Benzooxazol-2-yl-hydroxy-methyl)-3-phenyl-propyl]-2-cyclopropylmethylsulfonyl-0methyl-4-morpholin-4-yl-4-oxo-butyramide as a tan solid; LC/MS retention time 3.256min (TIC), m/z=584 (M+H).

EXAMPLE 66

(R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzoxazole-2-carbonyl)-propyl]-amide

(Compound 128)



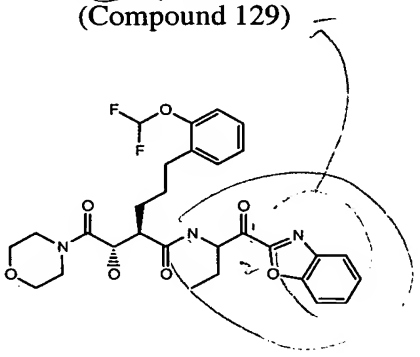
PyBOP (126 mg, 0.24 mmol), DIPEA (0.096 ml, 0.55mmol) and 2-Amino-1-benzooxazol-2-yl-butan-1-one hydrochloride (53 mg, 0.22 mmol) were added to a solution of (R)-2-((S)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid (70.7 mg, 0.22 mmol) in dry methylene chloride (5 ml) and the reaction mixture was stirred overnight at room temperature. The reaction was concentrated under reduced pressure, the residue

dissolved in ethyl acetate and washed with water. Organic extract was dried over $MgSO_4$ and evaporated under reduced pressure. Column chromatography on silica eluting with a mixture of ethyl acetate and heptane gave the title compound as white solid (38 mg); ^1H NMR ($CDCl_3$) δ 1.02 (t, J=7.4Hz, 3H), 1.97-1.62 (m, 5H), 2.21-2.15 (m, 1H), 2.74-2.59 (m, 3H), 3.65-3.49 (m, 8H), 4.41 (m, 1H), 4.70 (m, 1H), 5.62 (m, 1H), 6.93 (d, J=7.1Hz) 6.68 (d, J=7.1Hz, 1H), 7.33-7.13 (m, 5H), 7.49 (t, J=8Hz, 1H), 7.57 (t, J=8Hz, 1H), 7.66 (d, J=5.9, 1H), 7.92 (d, J=8Hz, 1H); MS: 508(MH^+); LC/MS retention time was 3.05 minutes.

EXAMPLE 67

(R)-5-(2-Difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid, 1-(benzoxazole-2-carbonyl)-propyl]-amide

(Compound 129)



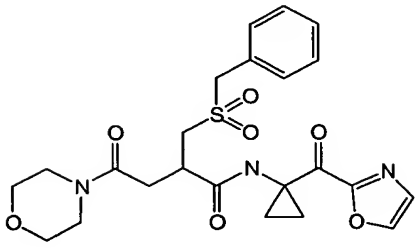
Similarly prepared according to the procedure in Example 66 but using (R)-5-(2-difluoromethoxy-phenyl)-2-((S)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid as the acidic component; ^1H NMR ($CDCl_3$) δ 1.06 (t, J=7.5Hz, 3H), 1.97-1.63 (m, 5H), 2.23-2.14 (m, 1H), 2.79-2.68 (m, 3H), 3.75-3.50 (m, 8H), 4.42 (m, 1H), 4.81-4.62 (m, 1H), 5.61 (m, 1H), 6.53 (t, J=74Hz, 1H), 6.73 (d, J=7.1Hz), 6.98 (d, J=7.1Hz, 1H), 7.24-7.06 (m, 4H), 7.59-7.49 (m, 2H), 7.69-7.64 (m, 1H), 7.91 (d, J=7.9Hz, 1H); MS: 574(MH^+).

EXAMPLE 68

4-Morpholin-4-yl-N-[1-(oxazole-2-carbonyl)-cyclopropyl]-4-oxo-2-benzylsulfonyl

methyl –butyramide

(Compound 130)



Similarly prepared according to the procedure in Example 66 but using 4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyric acid as the acidic component and (1-Amino-cyclopropyl)-oxazol-2-yl-methanone hydrochloride as the basic component; MS: 490 (MH^+); LC/MS, retention time 2.44 minutes.

EXAMPLE 69

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM). Human cathepsin S (0.158 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Val-Val-Arg-AMC (9 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 70

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: *N*,*N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-FR-AMC (20 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 71

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 72

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested according to the above-described assays for protease inhibition and observed to exhibit selective cathepsin S inhibitory activity. For example, the compounds of the invention were found to inhibit cathepsin S protease activity at concentrations that are least 50 fold less than those concentrations required to produce an equiactive inhibition of cathepsin K protease activity. The apparent inhibition constants (K_i) for compounds of the invention, against Cathepsin S, were in the range from about 10^{-10}M to about 10^{-7}M.

EXAMPLE 73

Representative Pharmaceutical Formulations Containing a Compound of Formula I

ORAL FORMULATION

Compound of Formula I	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

Compound of Formula I	0.1-10 mg

Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

Compound of Formula I	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.